

Europäisches **Patentamt** 

European **Patent Office**  Office européen des brevets

Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application conformes à la version described on the following page, as originally filed.

Les documents fixés à cette attestation sont initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patent application No. Demande de brevet no Patentanmeldung Nr.

04025035.9

Der Präsident des Europäischen Patentamts;

For the President of the European Patent Office

Le Président de l'Office européen des brevets p.o.

R C van Dijk



Anmeldung Nr:

Application no.:

04025035.9

Demande no:

Anmeldetag:

Date of filing: 21.10.04

Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

B&B Beheer NV Alkerstraat 28 3570 Alken BELGIQUE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention: (Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung. If no title is shown please refer to the description. Si aucun titre n'est indiqué se referer à la description.)

Use of D4 and 5-HT2A antagonists, inverse agonists or partial agonists

In Anspruch genommene Prioriät(en) / Priority(ies) claimed /Priorité(s) revendiquée(s) Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

EP/02.12.03/EP 03447279 EP/05.01.04/EP 04447001 EP/18.03.04/EP 04447066

Internationale Patentklassifikation/International Patent Classification/Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR LI

10

15

20

# USE OF D4 AND 5-HT2A ANTAGONISTS, INVERSE AGONISTS OR PARTIAL AGONISTS

#### Field of the invention

The invention relates to the field of neuropsychiatry. More specifically, the invention relates to the use of compounds, which have D4 and 5-HT2A antagonist, inverse agonist or partial agonist activity, for the preparation of medicaments.

#### Background of the invention

Conventionally, mental disorders are divided into types based on criteria sets with defining features. DSM-IV (American Psychiatric Association, (1993 – ISBN 0 – 89042 – 061 – 0)) is the in the art well-known golden standard of such a categorical classification. In DSM-IV, there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder. There is also no assumption that all individuals described as having the same mental disorder are alike in all important ways. Individuals sharing a diagnosis are likely to be heterogeneous even in regard to the defining features of the diagnosis. Thus, the categorical defined mental disorders as mood and anxiety disorders are having an external and even internal variable co-incidence of symptoms concerning e.g. mood, anxiety, perception, feeding, somatic sensations, sexual functions, sleep, cognitive functioning, impulse control, attention, substance use, personality, bereavement, identity, phase of life, abuse or neglect and other aspects of behavior.

In a <u>dimensional system</u>, clinical presentations are classified based on quantification of attributes i.e. dysfunctions rather than the assignment to categories and works best in describing phenomena that are distributed continuously and that do not have clear boundaries.

Emotion dysregulation is known as such an attribution or dysfunction that plays an important role in the development and course of mental disorders (Gross, J. J. & Munoz, R. F., 1995, Emotion regulation and mental health, Clinical Psychology: Science and Practice, 2, 151-164; Mennin, D.S., Heimberg, R. G., Turk, C. L. & Fresco, D. M., 2002, Applying an emotion regulation framework to integrative approaches to generalized anxiety disorder, Clinical Psychology: Science and Practice, 9, 85-90; Linehan, M. M., 1993, Cognitive-behavioral treatment of borderline personality disorder, New York, The Guilford Press; Gratz, K. L., Roemer, L., 2001 & 2004, Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation

10

15

20

25

... AT 11A 1000A 00+00

of the Difficulties in Emotion Regulation Scale, Annual meeting of the Association for Advancement of Behavior Therapy, Nov. 2001 & Journal of Psychopathology and Behavioral Assessment, Vol. 26, No. 1, March 2004) besides behavioural and cognitive dysfunctions. D4 dopamine receptors (D4DR), almost exclusively present in the mesocortical and mesolimbic systems (O'Malley, K. L., Harmon, S., Tang, L., Todd, R. D., The rat dopamine D4 receptor: sequence, gene structure, and demonstration of expression in the cardiovascular system, New Biol., 4, 137-46, 1992), are in the art known as modulators of emotion and cognition. D4DR agonistic activity gives a behavioural sensitisation; D4DR antagonistic activity leads to an emotion modulation (Svensson, T. H., Mathé, A. A., Monoaminergic Transmitter Systems, Biological Psychiatry (eds. D'Haenen, H., et al.), 45-66, 2002, John Wiley & Sons, Ltd). Data demonstrate that agonism of the dopamine D4 receptors play an important role in the Induction of behavioral sensitization to amphetamine and accompanying adaptations in pre- and postsynaptic neural systems associated with the mesolimbocortical dopamine projections (D. L. Feldpausch et al.; The Journal of Pharmacology and Experimental Therapeutics Vol. 286, Issue 1, 497-508, July 1998).

Results suggest that the antagonisms of cortical D2 dopamine receptors are a common target of traditional and atypical antipsychotics for therapeutic action. Higher *in vivo* binding to the D2 receptors in the cortex than in the basal ganglia is suggested as an indicator of favorable profile for a putative antipsychotic compound (*X. Xiberas and J.L. Martinot; The British Journal of Psychiatry (2001) 179: 503-508)*. Results show that dopamine D4 receptor antagonism in the brain does not result in the same neurochemical consequences (increased dopamine metabolism or hyperprolactinemia) observed with typical neuroleptics (*Smita Patel et al., The Journal of Pharmacology and Experimental Therapeutics Vol. 283, Issue 2, 636-647,1997)*. The selective D4 dopamine receptor antagonist L-745,870 was ineffective as an antipsychotic for the treatment of neuroleptic responsive patients with acute schizophrenia (*Kramer, M.S. et al., Arch. Gen. Psychiatry 1997 Dec; 54(12):1080*).

Finally, in the biological system, mental disorders are defined on other levels of abstraction than in the categorical and dimensional system. Structural pathology (e.g. amyloid plaques in Alzheimer Disease), etiology (e.g. HIV Dementia) and deviance from a physiological norm (e.g. reduced cerebral blood flow) are often used as indicative biological markers for a mental disorder. The underlying dysregulation of various neurotransmittor systems (glutaminergic, GABAergic, cholinergic, monoaminergic (nor-

adrenergic, dopaminergic, serotonergic), etc.) is the in the art used model for the explanation of the biological determinants of the clinical presentation of mental disturbances. It is known that the Serotonin 2A Receptor (5-HT2A receptor) - which is widespread in the Central Nervous System (CNS) - has a regulating role on the dysregulation of various neuro-transmittor systems. 5-HT2A agonism gives several behavioural disturbances; 5-HT2A antagonism leads to a governance of mood, social behaviour, anxiety, cognitive function, stress, sleep functions, nociception, sexual functions, feeding and other aspects of behaviour (J.E. Leysen (2004) 5-HT2 Receptors; Current Drug Targets - CNS & Neurological Disorders, 2004, 3, 11-26).

10

15

25

30

35

5

Dysregulation of the HPA axis (hypothalamic - pituitary - adrenal axis) has frequently been reported in patients with psychiatric disorders, and is among the most robustly demonstrated neurobiological changes among psychiatric patients (D.A. Gutman and C.B. Nemeroff, Neuroendocrinology, Biological Psychiatry (eds. D'Haenen, H., et al), 99, 2002, John Wiley & Sons, Ltd). The resulting elevated plasma cortisol concentrations leads to an enhanced binding of serotonin for the 5-HT2A receptor (E. A. Young, Mineralocorticoid Receptor Function in Major Depression, Arch Gen Psychiatry, Jan 2003; 60: 24 - 28) and thus agonism.

Additionally 5-HT2A antagonism gives a des-inhibiting of the inhibitory effect of the 5-HT2A receptor on (i) the 5-HT1A receptor stimulation by serotonin (S. M. Stahl, Newer 20 Antidepressants and Mood Stabilizers, Essential Psychopharmacology, 265, University Press; 2 edition (June 15, 2000); ISBN: 0521646154) and on (ii) the dopamine release in the mesocortical systems (S. M. Stahl, Classical Antidepressants, Serotonin Selective and Noradrenargic Reuptake Inhibitors, Essential Psychopharmacology, 233, University Press; 2 edition (June 15, 2000); ISBN: 0521646154).

Clinical or real effectiveness of psychopharma is very rare via common pooping-out; many treatment-refractory patients and up to half of patients fail to attain remission (S. M. Stahl. Essential Psychopharmacology, Depression and Bipolar Disorders, 151, University Press; 2 edition (June 15, 2000); ISBN: 0521646154) . Implications of not attaining remission for Mental Disorders are increased relapse rates, continuing functional impairment and increased suicide rate (S. M. Stahl, Essential Psychopharmacology, Depression and Bipolar Disorders, 152, University Press; 2 edition (June 15, 2000); ISBN: 0521646154). Clinical causes of not attaining remission by the Current Psychopharmacological Compounds are inadequate early treatment, underlying emotion dysregulation (affecting instability - hypersensitivity - hyperaesthesia - dissociative phenomena, etc.) and

competitive antagonism. There is thus a growing need for a more efficient therapy and more efficient, selective and efficacious medicaments for treating mental disorders.

#### Summary of the invention

15

20

25

The present invention relates to the use of compounds and pharmaceutical compositions having D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity for the treatment of the underlying emotion dysregulation of mental disorders (e.g. affecting instability – hypersensitivity – hyperaesthesia – dissociative phenomena - etc.) and to methods entailing administering to a patient diagnosed as having a mental disorder a pharmaceutical composition containing (i) compounds having specific high selective D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity and (ii) a known medicinal compound and/or compositions of compounds. The combined D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic effects may reside within the same chemical or biological compound.

Taken into account the above mentioned (i) rare clinical or real effectiveness of psycho tropics, (ii) the governance of the features and dysfunctions responsible - in a variable co-incidentally — for the clinical state of the mental disorders by D4 dopamine receptor (D4DR) and 2A serotonin receptor (5-HT2A) antagonism and (iii) the fact that 5-HT2A antagonism gives a des-inhibiting of the inhibitory effect of the 5-HT2A receptor on (a) the 5-HT1A receptor stimulation by serotonin and on (b) the dopamine release in the mesocortical systems, the present invention relates to the use of a compound for the preparation of a medicament for treating a disease or disorder with an underlying emotion dysregulation, characterised in that said compound has (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors and wherein said compound is administered to a patient in a dose ranging between 5 and 15 mg of the active ingredient. Preferably, said compound is pipamperon.

In a preferred embodiment, in a mono therapeutic context, the invention relates to the use of a compound as defined above, preferably pipamperon, for preparing a medicament for treating a disease or disorder selected from the group comprising anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment

10

15

20

25

5

disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational, identity, phase of life, academic problem, problems related to abuse or neglect.

According to a further embodiment the invention relates to the use of a first compound as defined above for the preparation of a medicament for treating a mental disease or disorder with an underlying emotion dysregulation whereby a second compound is administered simultaneously with, separate from or sequential to said first compound to augment the therapeutic effect of said second compound on said disease, or to provide a faster onset of the therapeutic effect of said second compound on said disease.

The mental diseases or disorders characterized by an underlying emotion dysregulation can be grouped into subclasses as follows: (i) non-cognitive mental disorders comprising mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem. academic problem and problems related to abuse or neglect; (ii) cognitive diseases comprising delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders; (iii) pain disorders; and (iv) Parkinson Disease.

In a preferred embodiment, the first compound is administered daily at least one day before administering said second compound.

30 Preferably, said second compound is characterized by the physiological property of influencing positively the activity of the Central Nervous System.

The invention also relates to a method for preparing a compound having a selective D4 and 5-HT2A antagonist, reverse agonist or partial agonist activity comprising the following steps: (a) measuring the selective affinity of a test compound to the D4 receptor and

10

15

20

25

30

6

selecting a compound that has a pKi value equal to or greater than 8 towards the D4 receptor in respect to all the other D receptors, and measuring the selective efficacy of the selected compound to the D4 receptor and selecting a compound which is a selective antagonist, inverse agonist or partial agonist of the D4 receptor; (b) measuring the selective affinity of a test compound to the 5-HT2A receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the 5-HT2A receptor in respect to all the other 5HT receptors, and measuring the selective efficacy of the selected compound to the 5-HT2A receptor and selecting a compound which is a selective antagonist, inverse agonist or partial agonist of the 5-HT2A receptor; (c) identifying a compound which is selected in (a) and (b), (d) preparing the compound identified in (c).

The invention further also relates to a compound prepared by the described method.

#### Detailed description of the invention

The present inventors surprisingly found that compounds which have a high selective affinity towards the 5-HT2A receptor and which, at the same time have a high selective affinity towards the dopamine-4 (D4) receptor show an improved effect in treating underlying emotion dysregulation of mental disorders.

The compounds according to the invention may be chemical or biological in nature, or may be chemically synthesised. Preferably, the compounds of the invention are provided as a pharmaceutically acceptable salt.

One example of such a compound which has both a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors, and a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors is pipamperon. Pipamperon is the conventional name given for the compound of the formula 1'-[3-(p-Fluorobenzoyl)propyl]-[1,4'-bipiperidine]-4'-carboxamide. Pipamperon is also the active ingredient of for instance the commercially available Dipiperon (Janssen, Cilag B.V).

Further, the present inventors surprisingly found that the dosage of active ingredient for pipamperon in treatment (in monotherapy as well as in combination therapy as described in more detail further) could be very low compared to conventionally used dosages. Preferred dosages which, according to the invention, have been shown to be effective for treating these mental disorders, range between 5 and 15 mg per day or between 5 and 10

20

25

30

1 . - A1 /10 /0004 0000

7

mg per day. More preferably, dosages of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 mg per day are used in treatment of the diseases of the invention. In conventional pipamperon treatment, the active ingredient is available in tablets of 40 mg per tablet or in solutions of 2 mg per drop. Conventional usage of high doses ranging from 40 to 360 mg is prescribed. For instance, for children up to the age of 14, doses corresponding with 2 to 6 mg per kg body weight are conventionally prescribed. The high selective affinity of pipamperon towards the 5-HT2A receptor and the D4 receptor is reflected in the tow dosage which is needed for the treatment of the mental diseases listed below and also contributes to the efficacy of the treatment.

10 The mental disorders which can be treated using pipamperon in a mono therapy at such low doses are for instance anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational, identity, phase of life, academic problem, problems related to abuse or neglect.

Mental disorders such as depression are commonly treated with serotonin re-uptake inhibitors. Unfortunately, however, these compounds can give rise to side affects in use. Moreover, a substantial problem in most treatment of mental disorders is a non-response to selective serotonin re-uptake inhibitors (SSRIs). Also the onset of the therapeutic effect can be delayed undesirable.

A problem to be solved by the present invention is thus the provision of a more efficient therapy and efficient, highly selective and efficacious medicaments for treating mental disorders.

The inventors found that, for instance, the non-response to selective serotonin re-uptake inhibitors (SSRIs) in depression may be declared by (partial) inhibition of the 5-HT1A stimulation via 5-HT2A stimulation. Des-inhibition thereof via 5-HT2A antagonism seems to be an answer to this problem.

The present inventors found that a simultaneous or foregoing treatment with a compound having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity, could lead to a greater response towards, for instance, SSRIs. However, not all compounds exhibiting 5-HT2A antagonism are useful: competition between 5-HT2A stimulation via

serotonin and 5-HT2A antagonism via the compound could be responsible for the lack of more efficacy of compounds which have both a selective serotonin re-uptake inhibitory and 5-HT2A antagonist profile, such as trazodone and nefazodone.

The present inventors further surprisingly found that a simultaneous or foregoing treatment with a compound having a high selective D4 antagonist, inverse agonist or partial agonist activity in combination with a compound having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity could lead to a greater response towards, for instance, SSRIs.

5

10

15

.20

25

30

In this invention, the term "antagonist" refers to an interaction between chemicals in which one partially or completely inhibits the effect of the other, in particular agents having high affinity for a given receptor, but which do not activate this receptor.

In this invention, the term "inverse agonist" refers to a ligand which produces an effect opposite to that of the agonist by occupying the same receptor.

In this invention, the term "agonist" relates to an agent which both binds to a receptor and has an intrinsic effect.

In this invention, the term "partial agonist" relates to an agent with lower intrinsic activity than a full agonist, and which produces a lower maximum effect.

The present inventors found that a compound which binds to the 5-HT2A receptor with a pKi of at least 8 but for which the binding affinity, i.e. pKi, towards other 5HT receptors is less than 8 in combination with a high selective affinity for the D4 receptor, i.e. which bind to the D4 receptor with a pKi of at least 8 but for which the binding affinity, i.e. pKi, towards other dopamine receptors is less than 8 also show such an improved effect in treatment. These effects, i.e. D4 antagonism, inverse agonism or partial agonism and 5-HT2A antagonism, inverse agonism or partial agonism, may reside in the same compound.

The term "other 5HT receptors" as used herein relate to for instance 5-HT1 receptors (e.g. 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F), 5-HT2B, 5-HT2C, 5-HT6 (rat) and 5-HT7 (rat).

By the expression "selective affinity for the 5-HT2A receptor" is meant that the receptor has a higher affinity for the 5-HT2A receptor than for other 5-HT receptors.

The expression "selective affinity for the D4 receptor" means that the receptor has a higher affinity for the dopamine D4 receptor than for other dopamine receptors.

15

30

9

The term "other dopamine receptors" are, for instance, D1, D2 and D3 dopamine receptors.

pKi values of test compounds for dopamine receptors as well as 5-HT2A receptors can be measured using commonly known assays.

Compounds which have a selective affinity for the D4 receptor preferably have a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors.

Preferably, the compounds of the invention which have a selective affinity for the 5-HT2A receptor (or the D4 receptor), are compounds which have a pKi value equal to or higher than 8 towards the 5-HT2A receptor and the D4 receptor, and less than 8 towards other 5-HT receptors or dopamine receptors, respectively, as can be measured, for instance by methods known in the art. For instance, the "NIMH Psychoactive Drug Screening Program (PDSP)" K<sub>I</sub> database (http://kidb.cwru.edu/nimh/5htp.php), is a unique resource in the public domain which provides information on the abilities of drugs to interact with an expanding number of molecular targets. The PDSP K<sub>I</sub> database serves as a data warehouse for published and internally-derived pKi, or affinity, values for a large number of drugs and drug candidates at an expanding number of G-protein coupled receptors, ion channels, transporters and enzymes. The PDSP internet site also provides for commonly used protocols and assays for measuring pKi values of 5-HT and dopamine receptors.

A preferred example of a compound which has both a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors, and a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors and which is therefore useful in a combination therapy is pipamperon.

Table 1 illustrates the selective affinity of for instance pipamperon for the 5-HT2A and for the D4 receptor. In addition, Table 1 also illustrates the low or absence of affinity of pipamperon for other receptors such as the adrenergic receptors Alpha 1A, Alpha 2A, Alpha 2B, Alpha 2C, Beta 1, Beta 2, and the histamine receptor H1. As such, treating patients with pipamperon will provide for less side effects which otherwise result from simultaneous stimulation of other receptors. Therefore, and according to preferred embodiments, useful compounds according to the invention not only have a selective 5-HT2A and/or D4 affinity but also a low affinity for other receptors such as the adrenergic and histamine receptors.

10

15

20

35

The low dosage which can be used in pipamperon treatment, as already described earlier, contributes to the high selective affinity of the compound towards the 5-HT2A receptor and the D4 receptor and therefore also to the efficacy of the treatment.

The mental diseases or disorders characterized by an underlying emotion dysregulation can be grouped into subclasses as follows: (i) the non-cognitive mental disorders comprising mood disorders, anxiety disorders, psychotic disorders, eating disorders. premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders. adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders. personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect; (ii) cognitive diseases comprising delirium, Alzheimer Disease, substance-related persisting dementia. vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfedt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders; (iii) the pain disorders; and (iv) Parkinson Disease. In Table 5, this classification has been used for summarizing the diseases and disorders relative to known psychotropics. In Table 6, an overview of pharmacological grouping is provided, indicating the pharmalogical profile numbering, the pharmalogical profile, the main disease or disorder indication(s), the name of the compound, the dose range, and the company producing or selling said compound.

These diseases and their diagnosis are very clearly defined in the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)" published by the American Psychiatric Association. This manual sets forth diagnostic criteria, descriptions and other information to guide the classification and diagnosis of mental disorders and is commonly used in the field of neuropsychiatry. It is for instance available on the internet under:

http://www.behavenet.com/ capsules/disorders/ dsm4tr.htm.

The expression "non-cognitive diseases or disorders" used in some of the embodiments of the invention comprises the following group of diseases or disorders: mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

10

15

20

25

30

35

11

impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect.

In other embodiments of the invention, the mental diseases or disorders that are characterized by an underlying emotion dysregulation belong to the group of pain disorders. For instance, the combination therapy with pipamperon is especially advantageous for management of acute pain in diseases such as, but not limited to, musculoskeletal diseases, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. For the classification of pain disorders, reference is also made to the DSM-IV where these disorders are clearly described in the section of somatoform disorders by way of internationally accepted diagnostic criteria.

In other embodiments of the invention, the 5-HT2A receptor and/or Dopamine-4 receptor antagonist, inverse agonist or partial agonist (e.g. pipamperon) is used in treatment of patients having neuro-degenerative diseases or disorders, or related cognitive diseases or disorders. The diseases or disorders of the present invention are characterized by an underlying degeneration of the Central Nervous System (CNS), preferably selected from the group consisting of, but not limited to, neurodegenerative diseases such as Parkinson Disease, and in other embodiments of the invention, selected from the group of (related) cognitive diseases or disorders such as Alzheimer Disease.

For instance, Parkinson Disease, which is a chronic progressive nervous disease chiefly of later life, is linked to decreased dopamine production in the substantia nigra and Is marked by tremor and weakness of resting muscles and by a shuffling gait. Dopamine agonists and even levodopa, widely used in Parkinson Disease, gives via a dopamine D4 receptor stimulation psychiatric manifestations. The induced release of serotonin acts via 5-HT2A stimulation as a "brake" on dopamine release (Young B.K., Camicioli R., Ganzini L., Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. Drugs Aging. 1997 May;10(5):367-83). Because of the need of specific D4 and 5-HT2A antagonism in the treatment of Parkinson Disease with dopamine agonists and even levodopa, it seems reasonable to combine with a compound with a high selective D4 and 5-HT2A antagonism i.e. having merely no activity towards the other receptors especially the D2 receptor because of the primary need of the relieve of the excessive burden of remaining dopaminergic neurons. Therefore, the use of the so-called atypical anti-psychotics or serotonin-dopamine antagonists (SDAs) is absolutely contra-

10

15

20

25

30

35

12

indicated since their high affinity for the D2 receptor. Even the use of serotonin releasing compounds such as SSRIs in the absence of an effective 5-HT2A antagonism are contraproductive towards the Parkinson Disease symptoms although many Parkinson patients are in need for an antidepressant since major depression is a very common and disabling condition in this kind of patients.

The expression "(related) cognitive diseases or disorders" according to the invention comprises, the following group of diseases or disorders: delirium (F05), dementia (such as Alzheimer Disease (F00), vascular dementia (F01), dementia due to other general medical conditions (HIV disease (F02.4), head trauma (F06.8), Parkinson Disease (F02.3), Huntington Disease (F02.2), Pick Disease (F02.0), Creutzfeldt-Jacob Disease (F02.1) and other (F02.8)), substance-induced persisting dementia (F1x.6)), amnestic disorders due to a general medical condition (F06.8) or a substance-induced persisting amnestic disorder (F1x.6), mild cognitive impairment disorder (F06.7) and other cognitive disorders (F04). The above list of diseases is provided by way of example and is not intended to limit the invention.

For instance, Alzheimer Disease is a degenerative brain disease of unknown cause that is the most common form of dementia. Alzheimer Disease usually starts in late middle age or in old age as a memory loss for recent events spreading to memories for more distant events and progresses over the course of five to ten years to a profound intellectual decline characterized by dementia and personal helplessness. The disease is marked histologically by the degeneration of brain neurons especially in the cerebral cortex and by the presence of neurofibrillary tangles and plaques containing beta-amyloid. Because dopamine receptor D4 (DRD4) antagonism can inhibit the behavioral disturbances merely aggression and confusion - caused by the degeneration of dopamine D2 receptors (Esiri, M.M., The basis for behavioural disturbances in dementia, J. Neurol. Neurosurg. Psychiatry, 1996; 61(2):127-130.2) accompanied with Alzheimer disease and 5-HT2A antagonism has an important boosting effect towards the effect of cholinesterase inhibitors such as used in the treatment by facilitating the affected dopamine release in the mesocortical dopamine pathways, a high selective D4/5-HT2A-antagonist would be a more preferable compound to combine with a cholinesterase inhibitor since this avoids the counteracting effect of the in the art used SDAs on the cognitive functioning by its dopamine receptor D2-antagonism.

These diseases and their diagnoses are very clearly defined in the "International Statistical Classification of Diseases and Related Health Problems, 1989 Revision, Geneva, World Health Organization, 1992 (ICD-10). This manual sets forth diagnostic

10

15

20

25

30

35

13

criteria, descriptions and other information to guide the classification and diagnosis of neurodegenerative disorders and is commonly used in the field of neurology. According to the ICD-10 classification, the cognitive disorders are classified under several classes of disorders, i.e. dispersed under categories F00 to F19 (see above: respective classification between parentheses). Following the DSM classification, however, they are grouped in one class of diseases or disorders.

The terms "treatment", "treating", and the like, as used herein include amelioration or elimination of a developed mental disease or condition once it has been established or alleviation of the characteristic symptoms of such disease or condition. As used herein these terms also encompass, depending on the condition of the patient, preventing the onset of a disease or condition or of symptoms associated with a disease or condition. including reducing the severity of a disease or condition or symptoms associated therewith prior to affliction with said disease or condition. Such prevention or reduction prior to affliction refers to administration of the compound or composition of the invention to a patient that is not at the time of administration afflicted with the disease or condition. "Preventing" also encompasses preventing the recurrence or relapse-prevention of a disease or condition or of symptoms associated therewith, for instance after a period of improvement. It should be clear that mental conditions may be responsible for physical complaints. In this respect, the term "treating" also includes prevention of a physical disease or condition or amelioration or elimination of the developed physical disease or condition once it has been established or alleviation of the characteristic symptoms of such conditions.

As used herein, the term "medicament" also encompasses the terms "drug", "therapeutic", "potion" or other terms which are used in the field of medicine to indicate a preparation with therapeutic or prophylactic effect.

The present inventors not only found that the selective 5-HT2A and D4 antagonists, inverse agonists or partial agonists have an effect in augmenting the therapeutic effect or in providing a faster onset of the therapeutic effect of a diversity of other pharmaceutical compounds, i.e. also named "second compounds" in the present invention, in the treatment of specific diseases or disorders. A few examples of other pharmaceutical compounds whose effects are augmented or where the onset of the effect is fastened upon simultaneous or fore-going treatment with a selective 5-HT2A and D4 antagonist, preferably pipamperon in a low dose, are nor-epinephrine re-uptake inhibitors, neuroleptic agents, dopamine antagonists, or compounds used for treating or alleviating musculoskeletal diseases or disorders. A further list of other pharmaceutical compounds

10

15

20

25

A ... ... ... ... ....

14

or second compounds useful according to the invention is provided in Table 5. It should be clear, given the general applicable character of the invention, that this list of other pharmaceutical compounds is very brief and that the invention should not be restricted to the ones exemplified herein. It should be clear that in the present invention, pipamperon is never to be seen as a "second compound".

According to the invention, it thus has been found that the compounds having a selective 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity as described above are useful for augmenting the therapeutic effect of a second compound on a disease.

According to another embodiment of the invention, it has also been found that the compounds having a selective 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity as described above are useful for providing a faster onset of the therapeutic effect of a second compound on a disease.

From the above it should be clear that the selective 5-HT2A and D4 antagonist, inverse agonist or partial agonist is also named 'the first compound' in the embodiments of the invention.

According to the invention, when the 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity reside in separate compounds, the term "composition" may be used. Compositions of the invention comprise a first element having (i) a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors, and a second element having (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT7 receptors.

The expression "the 5-HT2A and D4 antagonist, inverse agonist or partial agonist" is used herein to indicate a single compound having both activities or to indicate the composition comprising the activities in separate elements.

It should be clear that when, in the present invention, a composition of separate elements is used instead of a single compound, this composition of separate elements may be used in combination with another, i.e. a second, compound to augment the therapeutic effect of the other, i.e. the second, compound on the same or another disease.

When the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements and the second compound are administered simultaneously, the compounds or active ingredients may be present in a single pharmaceutical composition or formulation. Alternatively the compounds or active ingredients are administered in separate pharmaceutical compositions or formulations for simultaneous or

15

15

separate use. The invention thus also relates to pharmaceutical compositions comprising pipamperon and a second compound of the invention and to the uses of these pharmaceutical compositions.

When the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements of the invention are administered prior to the second compound as defined, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements is administered at least during 1 day prior to said second compound. Preferably, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist (e.g. pipamperon) or the composition comprising both elements is administered for at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 days prior to the administration of the second compound. Preferably, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist (e.g. pipamperon) or the composition comprising both elements is administered for at least 2, 3, 4 or 5 weeks prior to the administration of the second compound, or even for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months prior to the administration of the second compound.

According to a preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of citalopram or for providing a faster onset of the therapeutic effect of citalopram.

- Citalopram or citalopram hydrobromide is a selective serotonin (5-hydroxytryptamine / 5-HT) re-uptake inhibitor (SSRI) and is the conventional name given for the compound of the formula (RS)-1-[3-(dimethylamino)propyl]-1-(p-flurophenyl)-5-phthalancarbonitrile hydro-bromide.
- According to an embodiment, a daily dose of active ingredient of SSRI, preferably citalopram, ranges between 10 and 40 mg per day. Preferably, daily doses of active ingredient ranging between 20 and 30 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

According to another preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of citalogram or for providing a faster onset of the therapeutic effect of fluvoxamine.

Fluvoxamine or fluvoxamine maleate (luvox, fevarin) is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime

10

15

20

25

30

16

ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1).

According to an embodiment, a daily dose of active ingredient of fluvoxamine maleate ranges between 100 and 300 mg per day. Preferably, daily doses of active ingredient ranging between 150 and 200 mg per day are administered. More preferably, a daily dose of 100, 150, 200, 250 or 300 mg per day is administered.

Most of the second compounds herein described are known in the art and may be used in doses according to the supplier's or physician's prescription, or may be used according to specific embodiments described herein.

Also encompassed by the invention are pro-drugs to these second compounds or active metabolites of these compounds. For instance, for risperidone it is known that, among other products, bio transformation in the liver produces 9-hydroxyrisperidone, which is of the same pharmacological activity and intensity as parent risperidone. Therefore, also 9-hydroxyrisperidone, naturally produced or chemically synthesized may be used in the methods and uses according to the invention.

The term "active metabolite" as used herein relates to a therapeutically active compound produced by the metabolism of a parent drug. Drugs administered to treat diseases are usually transformed (metabolized) within the body into a variety of related chemical forms (metabolites), some of which may have therapeutic activity (an active metabolite).

The present invention also encompasses the use of these second compounds, administered in the form of a pharmaceutically acceptable salt in admixture with a suitable pharmaceutically acceptable excipient.

To prepare the pharmaceutical compositions, comprising the compounds or the combination of the first and second compound described herein, an effective amount of the active ingredients, in acid or base addition salt form or base form, is combined in admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, for administration orally, nasal, rectally; percutaneously or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders,

- -----

10

15

20

25

30

17

disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included.

The pharmaceutical compounds for treatment are intended for parenteral, topical, oral or local administration and generally comprise a pharmaceutically acceptable carrier and an amount of the active ingredient sufficient to reverse or prevent the bad effects of mental disorders. The carrier may be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration.

Examples of pharmaceutically acceptable acid addition salts for use in the present inventive pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, p-toluenesulphonic acids, and arylsulphonic, for example.

The pharmaceutically acceptable excipients described herein, for example, vehicles, adjuvants, carriers or diluents, are well-known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one that is chemically inert to the active compounds and one that has no detrimental side effects or toxicity under the conditions of use.

The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration are merely exemplary and are in no way limiting. Overall, the requirements for effective pharmaceutical carriers for parenteral compositions are well known to those of ordinary skill in the art. See Pharmaceutics and Pharmacy Practice, J.B. Lippincott Company, Philadelphia, PA, Banker and Chalmers, eds., pages 238-250, (1982), and ASHP Handbook on Injectable Drugs, Toissel, 4th ed., pages 622-630 (1986). Topical formulations, including those that are useful for transdermal drug release, are well-known to those of skill in the art and are suitable in the context of the present invention for application to skin.

Formulations suitable for oral administration require extra considerations considering the nature of the compounds and the possible breakdown thereof if such compounds are administered orally without protecting them from the digestive secretions of the

10

15

20

25

30

35

18

gastrointestinal tract. Such a formulation can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid. microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide. croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are known in the art.

The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. For aerosol administration, the compounds are preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of compounds are 0.01%-20% by weight, preferably 1%-10%. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanolc, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1%-20% by weight of the compounds, preferably 0.25-5%. The balance of the compounds is ordinarily propellant. A carrier can also be included as desired, e.g., lecithin for intranasal delivery. These aerosol formulations can be placed into acceptable pressurized propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

Such spray formulations may be used to spray mucosa.

It will be understood that, apart from daily doses, the compounds can be administered by other schedules. For instance, the present invention also contemplates depot injection, in which a long acting form of the active compound is injected into the body, such as the muscles. From there the active compound slowly enters the rest of the body, so one injection can last from 1 to 4 weeks or even multiple months. Other form of dosage administrations relate to "once-a-week" pills, in which the ingredient is slowly released over a period of a week, and slow-realese patches, e.g. a CDS (Continuous Delivery System), or Once-a-Day Transdermal Patches.

According to a further embodiment, the invention also relates to a method for preparing a compound or composition having a selective D4 and 5-HT2A antagonist, reverse agonist or partial agonist. The invention also relates to the compounds prepared by the claimed method, with the proviso that said compound is not an already known compound, such as pipamperon.

It should be clear that the compounds and compositions described herein are useful for treating any patient in need thereof. As used herein the term "patient" is not restricted to humans but also to other mammals, for instance, domestic animals which may also suffer from any form of a mental disease or disorder described herein.

The second compounds of the invention can be further grouped according to their pharmacological profile, which is summarized in Table 6.

The present invention is now described in more detail by the following embodiments. The compounds belonging to different pharmacological profiles can be further grouped according to their action on the same pathway or system as follows.

# 1: combination therapy with a 5-HT (serotonin) reuptake enhancer

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT (serotonin) reuptake enhancer, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

15

20

25

30

35

20

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT (serotonin) reuptake enhancer compound is tianeptine or a prodrug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, tianeptine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT (serotonin) reuptake enhancer, preferably tianeptine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders. premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders. adjustment disorders, impulse control disorders, substance related disorder, personality disorder, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

A pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT (serotonin) reuptake enhancer is tianeptine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

#### 15 2: combination therapy with a 5-HT1 autoreceptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1 autoreceptor agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome. somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

25

30

35

20

21-10-04;19:53 ;DCB

5

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders). factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder. personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1 autoreceptor agonist compound to augment

the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1 autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1 autoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1 autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

20

10

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1 autoreceptor agonist compound is sunepitron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

25

30

35

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. and (b) a 5-HT1 autoreceptor agonist, preferably sunepitron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorder, antisocial behaviour, bereavement occupational problem, problems related to abuse or neglect and pain disorders.

3: combination therapy with a 5-HT1A (serotonin 1A receptor) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1A (serotonin 1A receptor) agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders.

10

15

20

25

30

35

23

premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention further also relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that

10

15

20

25

24

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention further also relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or sald pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention further also relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1A (serotonin 1A receptor) agonist compound is chosen from the group consisting of MN-305, zalospirone, xaliproden, VPI-013 (also known as OPC-14523), tandosprione, sarizotan, PRX-00023, metanospirone, lesopitron, gepirone, flesinoxan, EMD 68843, buspirone, bupropion (preferably controlled release formulation) and alnespirone, preferably xaliproden, sarizotan, gepirone, flesinoxan and bupropion (preferably controlled release formulation) or a pro-drug or an active metabolite thereof,

15

20

25

30

35

25

or a pharmaceutically acceptable salt thereof. More preferably, said 5-HT1A (serotonin 1A receptor) agonist is xaliproden and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient. Even more preferably, said 5-HT1A (serotonin 1A receptor) agonist is buproprion (controlled release formulation) and is to be administered in a daily dose ranging between 150 and 450 mg of the active ingredient. Even more preferably, said 5-HT1A (serotonin 1A receptor) agonist is gepirone and is to be administered in a daily dose, ranging between 20 and 80 mg of the active ingredient per day.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. and (b) a 5-HT1A (serotonin 1A receptor) agonist, preferably chosen from the group consisting of MN-305, zalospirone, xaliproden, VPI-013 (also known as OPC-14523). tandosprione, sarizotan, PRX-00023, metanospirone, lesopitron, gepirone, flesinoxan, EMD 68843, buspirone, bupropion (preferably controlled release formulation) and alnespirone, more preferably xaliproden, sarizotan, gepirone, flesinoxan and bupropion (preferably controlled release formulation), or a pro-drug or an active metabolite thereof. or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is xaliproden, preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

10

15

20

25

30

35

26

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is buproprion (controlled release formulation), preferably provided in a unitary dose of between 150 and 450 mg of the active ingredient.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is gepirone, preferably provided in a unitary dose of between 20 and 80 mg of the active ingredient.

### 4: combination therapy with a 5-HT1A (serotonin 1A receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1A (serotonin 1A receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

25

27

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1A antagonist compound is chosen from the group consisting of robalzotan tartrate hydrate and NAD299 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1A antagonist, preferably chosen from the group consisting of robalzotan tartrate hydrate and NAD299, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

#### 5: combination therapy with a 5-HT1B (serotonin 1B receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1B (serotonin 1B receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

30

35

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders.

15

20

25

30

35

adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT1B antagonist compound is chosen from the group consisting of elzasonan, AZD1134 and AR-A2, preferably elzasonan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1B antagonist, preferably chosen from the group consisting of elzasonan, AZD1134 and AR-A2, preferably elzasonan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

#### 6: combination therapy with a 5-HT2B (serotonin 2B receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT2B (serotonin 2B receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality

10

15

20

25

30

35

...... 110 /000 A 000 00

29

disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT2B antagonist compound is agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, agomelatine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT2B antagonist, preferably agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for

30

simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

A pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT2B antagonist is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

#### 7: combination therapy with a 5-HT2C (serotonin 2C receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT2C (serotonin 2C receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

25

30

35

15

20

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C antagonist compound to augment the therapeutic effect or to

20

25

30

35

1 . - A4 /4A /AAA A AAA AA

31

provide a faster onset of the the rapeutic effect of said 5-HT2C antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2C antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT2C antagonist compound is chosen from the group consisting of SB 243213 and agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, agomelatine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT2C antagonist, preferably chosen from the group consisting of SB 243213 and agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT2C antagonist is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

#### 8: combination therapy with a 5-HT3 (serotonin 3 receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT3 (serotonin 3 receptor) antagonist compound, are substance-related disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance-related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT3 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT3 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

20

25

30

35

10

5

According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT3 antagonist compound is ondansetron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, ondansetron is to be administered in a daily dose ranging between 8 and 32 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT3 antagonist, preferably ondansetron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of substance-related disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient, and wherein said 5-HT3 antagonist is ondansetron, preferably provided in a unitary dose of between 8 and 32 mg of the active ingredient.

#### 9: combination therapy with a 5-HT6 (serotonin 6 receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT6 (serotonin 6 receptor) antagonist compound, are chosen from the group of

15

20

25

30

35

33

diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease. dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 10 emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with. separate from or prior to the administration of a 5-HT6 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT6 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above. wherein said 5-HT6 antagonist compound is chosen from the group consisting of SB-271046, 742457 and 271046 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. and (b) a 5-HT6 antagonist, preferably chosen from the group consisting of SB-271046. 742457 and 271046 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-

Jacob Disease, amnestic disorders due to a general medical condition, substanceinduced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

## 5 10: combination therapy with an acetylcholinesterase inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an acetylcholinesterase inhibitor compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

15

20

25

30

35

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an acetylcholinesterase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said acetylcholinesterase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said acetylcholinesterase inhibitor compound is chosen from the group consisting of tacrine, rivastigmine tartrate, rivastigmine, physostigmine, phenserine tartrate, metrifonate, huperzine A, galantamine (preferably extended release formulation), donezepil, dichlorvos and anseculin hydrochloride, preferably tartrate, or a pro-drug or an

15

20

25

30

35

35

active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, rivastigmine tartrate is to be administered in a daily dose ranging between 3 and 12 mg of the active ingredient. Preferably, phenserine tartrate is to be administered in a daily dose ranging between 20 and 30 mg of the active ingredient. Preferably, galantamine (extended release formulation) is to be administered in a daily dose ranging between 8 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. and (b) an acetylcholinesterase inhibitor, preferably chosen from the group consisting of rivastigmine tartrate, tacrine, rivastigmine, physostigmine, phenserine tartrate, metrifonate, huperzine A, galantamine (preferably extended release formulation). donezepil, dichlorvos and anseculin hydrochloride, preferably tartrate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is rivastigmine tartrate, preferably provided in a unitary dose of between 3 and 12 mg of the active ingredient.

The invention further relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is phenserine tartrate, preferably provided in a unitary dose of between 20 and 30 mg of the active ingredient.

In addition, the invention relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is galantamine (preferably

10

15

20

36

extended release formulation), preferably provided in a unitary dose of between 8 and 24 mg of the active ingredient.

### 11: combination therapy with an adenosine A2a receptor antagonist compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an adenosine A2a receptor antagonist compound, is Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adenosine A2a receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adenosine A2a receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said adenosine A2a receptor antagonist compound is KW-6002 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, KW-6002 is to be administered in a daily dose ranging between 40 and 80 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an adenosine A2a receptor antagonist, preferably KW-6002 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is KW-6002, preferably provided in a unitary dose of between 40 and 80 mg of the active ingredient.

35

30

### 12: combination therapy with an adrenergic transmitter releaser

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an adrenergic transmitter releaser, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

10

15

20

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35

30

10

15

20

25

30

35

. . . AT 110 1000 1 00 . 00

According to a preferred embodiment, the invention relates to the uses as described above, wherein said adrenergic transmitter releaser compound is pipoxazole or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, pipoxazole is to be administered in a daily dose ranging between 30 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an adrenergic transmitter releaser, preferably pipoxazole, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said adrenergic transmitter releaser is pipoxazole, preferably provided in a unitary dose of between 30 and 60 mg of the active ingredient.

### 13: combination therapy with an alpha 1 adrenoreceptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an alpha 1 adrenoreceptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxlety disorders, eating

10

15

20

25

30

35

39

disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said alpha 1 adrenoreceptor antagonist compound is chosen from the group consisting of SDZ NVI 085 and flesinoxan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

10

15

20

25

30

35

40

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an alpha 1 adrenoreceptor antagonist, preferably chosen from the group consisting of SDZ NVI 085 and flesinoxan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and Parkinson disease.

#### 14: combination therapy with an alpha 2 adrenoreceptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an alpha 2 adrenoreceptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is

10

41

to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said alpha 2 adrenoreceptor antagonist compound is chosen from the group consisting of UK-14304, sunepitron, mirtazepine, idazoxan, fluparoxan, A75200 and (R)-A 75200, preferably sunepitron or idazoxan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, idazoxan is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

20

25

30

15

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an alpha 2 adrenoreceptor antagonist, preferably chosen from the group consisting of UK-14304, sunepitron, mirtazepine, idazoxan, fluparoxan, A75200 and (R)-A 75200, preferably sunepitron or idazoxan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient

10

15

20

25

30

35

42

and wherein said alpha 2 adrenoreceptor antagonist is Idazoxan, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

### 15: combination therapy with an AMPA receptor mediator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor mediator compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further

- / .774 0 001

15

20

25

43

characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said AMPA receptor mediator compound is chosen from the group consisting of ampakine ORG 24448/CX-619, ampakine CX-717, ampakine CX-691 and ampakine CX-516, preferably ampakine ORG 24448/CX-619, ampakine CX-717 or ampakine CX-691, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

10

15

20

25

44

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an AMPA receptor mediator, preferably chosen from the group consisting of ampakine ORG 24448/CX-619, ampakine CX-717, ampakine CX-691 and ampakine CX-516, preferably ampakine ORG 24448/CX-619, ampakine CX-717 or ampakine CX-691, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

# 16: combination therapy with an amphetamine compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an amphetamine compound, are attention-deficit disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention deficit disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an amphetamine compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said amphetamine compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

According to a preferred embodiment, the invention relates to the use as described above, wherein said amphetamine compound is methylphenidate (preferably administered by the transdermal system) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

5

10

15

20

25

30

35

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an amphetamine, preferably methylphenidate (preferably administered by the transdermal system) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of attention deficit disorders.

### 17: combination therapy with an amyloid aggregation-inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an amyloid aggregation-inhibitor compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an amyloid aggregation-inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said amyloid aggregation-inhibitor compound, further

25

30

35

46

characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

EPO Munchen

According to a preferred embodiment, the invention relates to the use as described above, wherein said amyloid aggregation-inhibitor compound is chosen from the group consisting of APAN and Alzhemed, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, Alzhemed is to be administered in a daily dose of between 200 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, 10 and (b) an amyloid aggregation-inhibitor, preferably chosen from the group consisting of APAN and Alzhemed, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer 15 Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substanceinduced persisting amnestic disorder, mild cognitive impairment disorder and other 20 cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said amyloid aggregation-inhibitor is Alzhemed, preferably provided in a unitary dose of between 200 and 300 mg of the active ingredient.

# 18: combination therapy with an androgen receptor modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an androgen receptor modulator compound, are sexual and gender identity disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered

simultaneously with, separate from or prior to the administration of an androgen receptor modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said androgen receptor modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said androgen receptor modulator compound is LGD2226 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an androgen receptor modulator, preferably LGD2226 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of sexual and gender identity disorders.

15

20

25

30

35

5

### 19: combination therapy with an beta 3 adrenore ceptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an beta 3 adrenoreceptor agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of

a beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

EPO Munchen

5

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

According to a preferred embodiment, the invention relates to the uses as described above, wherein said beta 3 adrenoreceptor agonist compound is SR 58611 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, 20 25

and (b) a beta 3 adrenoreceptor agonist, preferably SR 58611 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and...

pain disorders. 30

35

# 20: combination therapy with a calcium channel modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a calcium channel modulator compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia,

10

15

20

25

30

35

49

vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said calcium channel modulator compound is chosen from the group consisting of safinamide and MEM 1003, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

10

20

25

30

35

1 - - 01 /10 /000 / 00° 00°

50

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a calcium channel modulator, preferably chosen from the group consisting of safinamide and MEM 1003, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson disease.

### 21: combination therapy with a cannabioid receptor 1 (CB1) antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a cannabioid receptor 1 (CB1) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said

10

15

20

25

30

35

51

pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabioid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabioid receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabioid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabioid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabioid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabioid receptor 1 antagonist compound; further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said cannabioid receptor antagonist compound is SR 141716 or a prodrug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a cannabioid receptor antagonist, preferably SR 141716 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of

15

20

25

30

35

diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

# 22: combination therapy with a cathepsin K inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a cathepsin K inhibitor compound, are pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cathepsin K inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cathepsin K inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said cathepsin K inhibitor compound is 462795 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a cathepsin K inhibitor, preferably 462795 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain disorders.

# 23: combination therapy with a choline uptake enhancer compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a choline uptake enhancer compound, are chosen from the group of diseases or

- / -774 F) 001

10

15

20

25

30

35

53

disorders consisting of Alzheimer Disease, substance-related persisting dementia. vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a choline uptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said choline uptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above. wherein said choline uptake enhancer compound is MKC-231 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, MKC-231 is to be administered in a daily dose of between 20 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a choline uptake enhancer, preferably MKC-231 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,

# 65/ 71

25

30

35

...... 14A 1000 A 00000

54

dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein 5 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said choline uptake enhancer is MKC-231, preferably provided in a unitary dose of between 20 and 160 mg of the active ingredient.

#### 24: combination therapy with a COX-2 inhibitor compound 10

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance plpamperon, in a combination therapy with a COX-2 inhibitor compound, are pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically 15 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a COX-2 inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said COX-2 20 inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said COX-2 inhibitor compound is chosen from the group consisting of valdecoxib, rofecoxib, parecoxib, etoricoxib, COX 189, celecoxib and ABT-963, preferably parecoxib, etoricoxib or COX 189, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, parecoxib is to be administered in a daily dose of between 20 and 80 mg of the active ingredient. Preferably, etoricoxib is to be administered in a daily dose of between 20 and 120 mg of the active ingredient. Preferably, COX 189 is to be administered in a daily dose of between 100 and 800 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a COX-2 inhibitor, preferably chosen from the group consisting of valdecoxib, rofecoxib, parecoxib, etoricoxib, COX 189, celecoxib and ABT-963, preferably parecoxib,

etoricoxib or COX 189, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain disorders.

5

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is parecoxib, preferably provided in a unitary dose of between 20 and 80 mg of the active ingredient.

10

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is etoricoxib, preferably provided in a unitary dose of between 20 and 120 mg of the active ingredient.

15

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is COX 189, preferably provided in a unitary dose of between 100 and 800 mg of the active ingredient.

20

25: combination therapy with a COX-inhibiting nitric oxide donator (CINOD) compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a COX-inhibiting nitric oxide donator (CINOD) compound, are pain disorders.

25

30

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a COX-inhibiting nitric oxide donator (CINOD) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said COX-inhibiting nitric oxide donator (CINOD) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35

10

15

20

25

56

According to a preferred embodiment, the invention relates to the use as described above, wherein said COX-inhibiting nitric oxide donator (CINOD) compound is chosen from the group consisting of AZD4717 and AZD3582 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, AZD3582 is to be administered in a daily dose ranging between 93.75 and 750 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a COX-inhibiting nitric oxide donator (CINOD), preferably chosen from the group consisting of AZD4717 and AZD3582 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-inhibiting nitric oxide donator (CINOD) is AZD3582, preferably provided in a unitary dose of between 93.75 and 750 mg of the active ingredient.

## 26: combination therapy with a CRF1 (corticoid-releasing factor receptor 1) antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a CRF1 (Corticotropin-Releasing Factor receptor 1) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders,

15

20

57

personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said CRF1 antagonist compound is chosen from the group consisting of R121919, NBI-34041, elzasonan, CP-448,187, CP-154-526, AAG 561 and 723620, preferably R121919, elzasonan or AAG 561, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, R121919 is to be administered in a daily dose of between 5 and 80 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a CRF1 antagonist, preferably chosen from the group consisting of R121919, NBI-34041, elzasonan, CP-448,187, CP-154-526, AAG 561 and 723620, preferably R121919, elzasonan or AAG 561, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

10

15

20

25

30

58

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said CRF1 antagonist is R121919, preferably provided in a unitary dose of between 5 and 80 mg of the active ingredient.

### 27: combination therapy with a D1 (dopamine 1) receptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a D1 (dopamine 1) receptor agonist, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said D1 receptor agonist compound is DAS-431 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

# 70/ 71

:+3292802345

5

10

15

20

25

30

59

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D1 receptor agonist, preferably DAS-431 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

### 28: combination therapy with D2 (dopamine 2) receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for Instance pipamperon, in a combination therapy with D2 (dopamine 2) receptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders. adjustment disorders, impulse control disorders, pervasive development disorders. disruptive behaviour disorders, substance-related disorders, personality disorders. psychological factors affecting medical conditions, malingering, antisocial behaviour. bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20

25

30

35

... - A 11A 10AA 1 AA-AA

EPO Munchen

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically 10 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor 15 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said D2 receptor antagonist compound is chosen from the group consisting of bifeprunox, amisulpride aminosultopride and amisulpride, preferably bifeprunox, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D2 receptor antagonist, preferably chosen from the group consisting of bifeprunox, amisulpride aminosultopride and amisulpride, preferably bifeprunox, or a prodrug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders. personality disorders, psychological factors affecting medical conditions, malingering.

antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

### 29: combination therapy with D3 (dopamine 3) receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with D3 (dopamine 3) receptor antagonist, are chosen from the group of diseases or disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium and Parkinson disease.

15

20

25

30

35

10

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the

21-10-04;22:14

5

10

15

20

25

30

35

BII , TOZUZO4

62

therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said D3 receptor antagonist compound is chosen from the group consisting of BSF-201640 and PD 58491, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D3 receptor antagonist, preferably chosen from the group consisting of BSF-201640 and PD 58491, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related

/ +100 D 000

disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium and Parkinson disease.

### 5 30: combination therapy with a DA (dopamine) uptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a DA (dopamine) uptake inhibitor, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

10

15

30

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a DA uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA uptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a DA uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA uptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said DA uptake inhibitor compound is chosen from the group consisting of safinamide and GBR 12909, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D2 receptor antagonist, preferably chosen from the group consisting of safinamide and GBR 12909, or a pro-drug or an active metabolite thereof, or a

pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

5

### 31: combination therapy with an dopamine (receptor) agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an dopamine (receptor) agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

15

20

25

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

35

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said

dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15 According to a preferred embodiment, the invention relates to the uses as described above, wherein said dopamine (receptor) agonist compound is chosen from the group consisting of sumanirole, SLV 308, sarizotan, S32504, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation). pramipexole, DAB452, cabergoline, bromocriptine, alaptide amantadine, bromocriptine, cabergoline lisuride and pergolide, preferably sumanirole, rotigotine (preferably a Once-a-20 Day Transdermal Patch), pergolide or ropinirole HCL (preferably controlled-release formulation), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, sumanirole is to be administered in a daily dose of between 4 and 16 mg of the active ingredient. Preferably, rotigotine (Once-a-Day 25 Transdermal Patch) is to be administered in a daily dose of between 4.5 and 13.5 mg of the active ingredient. Preferably, ropinirole HCL (controlled-release formulation) is to be administered in a daily dose of between 0.75 and 24 mg of the active ingredient. Preferably, pergolide is to be administered in a daily dose of between 0.5 and 10 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a dopamine (receptor) agonist, preferably chosen from the group consisting of sumanirole, SLV 308, sarizotan, S32504, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation), pramipexole, DAB452, cabergoline, bromocriptine, alaptide amantadine, bromocriptine, cabergoline lisuride and pergolide, more preferably sumanirole, rotigotine (preferably a

~ ~~

30

35

15

20

25

30

· · · · 01 /10 /000 / 00 • 00

66

Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation) or pergolide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is sumanirole, preferably provided in a unitary dose of between 4 and 16 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is rotigotine (Once-a-Day Transdermal Patch), preferably provided in a unitary dose of between 4.5 and 13.5 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is ropinirole HCL (controlled-release formulation), preferably provided in a unitary dose of between 0.75 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is pergolide, preferably provided in a unitary dose of between 0.5 and 10 mg of the active ingredient.

10

15

20

25

67

# 32: combination therapy with a compound activating ERK (extracellular signal-related kinase)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound that activates ERK (extracellular signal-related kinase), are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound that activates ERK (extracellular signal-related kinase) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound that activates ERK (extracellular signal-related kinase), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound that activates ERK (extracellular signal-related kinase) is CPI-1189 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, CPI-1189 is to be administered in a daily dose of between 50 and 100 mg of the active ingredient.

35

1 . . AT 11A 10004 MANT

10

15

20

25

68

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound that activates ERK (extracellular signal-related kinase), preferably CPI-1189 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound that activates ERK (extracellular signal-related kinase) is CPI-1189, preferably provided in a unitary dose of between 50 and 100 mg of the active ingredient.

### 33: combination therapy with a GABA (gamma-aminobutyric acid) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA (gamma-aminobutyric acid) agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders...

30

35

E--4 --: + + 01 /10 /0004 00+01

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,

EPO Munchen

dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

30

35

5

According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA agonist compound is nefiracetam or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable sait thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA agonist, preferably nefiracetam or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

### 34: combination therapy with a GABA-A agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for the form of the form of

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of sleep disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate

from or prior to the administration of a GABA-A agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-A agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-A agonist compound is gaboxadol or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, gaboxadol is to be administered in a daily dose of between 5 and 20 mg of the active ingredient.

10

15

20

25

30

35

. . . 01 /10 /000 4 00 - 01

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an GABA-A agonist, preferably gaboxadol or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of sleep disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A agonist is Gaboxadol, preferably provided in a unitary dose of between 5 and 20 mg of the active ingredient.

# 35: combination therapy with a GABA-A modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA-A (gamma-aminobutyric acid receptor A) modulator compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious

disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-A modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-A modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

25

30

35

According to a preferred embodiment, the invention relates to the use as described above. wherein said GABA-A modulator compound is chosen from the group consisting of zolpidem (preferably MR sustained-release version), zaleplon (preferably extendedrelease formulation), SL 65.1498, SEP174559, pagoclone, NGD 96-3, indiplon. eszopiclone, CP-730,330 (NGD 96-3) and ocinaplon, preferably zolpidem (preferably MR sustained-release version), zaiepion (preferably extended-release formulation). pagoclone, NGD 96-3, indiplon or eszopiclone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, zolpidem MR sustainedrelease version is to be administered in a daily dose of between 10 and 20 mg of the active ingredient. Preferably, zaleplon extended-release is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient. Preferably, pagoclone is to be administered in a daily dose ranging between 7.5 and 60 mg of the active ingredient. Preferably, indiplon is to be administered in a daily dose of between 10 and 20 mg of the active ingredient. Preferably, eszopiclone is to be administered in a daily dose of between 2 and 3 mg of the active ingredient. Preferably, ocinaplon is to be administered in a daily dose of between 10 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA-A modulator, preferably chosen from the group consisting of zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), SL 65.1498, SEP174559, pagoclone, NGD 96-3, indiplon, eszopiclone, CP-730,330 (NGD 96-3) and ocinaplon, preferably zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), pagoclone, NGD 96-3, indiplon or eszopiclone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental

10

15

20

25

30

35

72

disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is zolpidem MR sustained-release version, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is zaleplon extended-release, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is Pagoclone, preferably provided in a unitary dose of between 7.5 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is indiplon, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is eszopiclone, preferably provided in a unitary dose of between 2 and 3 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is ocinaplon, preferably provided in a unitary dose of between 10 and 60 mg of the active ingredient.

10

15

20

25

30

35

73

#### 36: combination therapy with a GABA-B antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA-B (gamma-aminobutyric acid receptor B) antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active Ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-B antagonist compound is AVE 7398 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA-B antagonist, preferably AVE 7398 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform

disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

5

### 37: combination therapy with a Glial-cell Line Derived Neurotrophic Factor compound The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a Glial-cell Line Derived Neurotrophic Factor compound, is Parkinson disease.

10

15

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a Glial-cell Line Derived Neurotrophic Factor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said Glial-cell Line Derived Neurotrophic Factor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20

25

30

35

According to a preferred embodiment, the invention relates to the use as described above. wherein said Glial-cell Line Derived Neurotrophic Factor compound is GDNF or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, GDNF is to be administered in a daily dose ranging between 3.75 and 30 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. and (b) a Glial-cell Line Derived Neurotrophic Factor, preferably GDNF or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said Glial-cell Line Derived Neurotrophic Factor is GDNF, preferably provided in a unitary dose of between 3.75 and 30 mg of the active ingredient.

#### 38: combination therapy with a glucocorticold synthesis inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a glucocorticoid synthesis inhibitor compound, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glucocorticoid synthesis inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glucocorticoid synthesis inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glucocorticoid synthesis inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glucocorticoid synthesis inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said glucocorticoid synthesis inhibitor compound is metyrapone or a prodrug or an active metabolite thereof, or a place-utically acceptable salt thereof.

The invention also relates to a pharmaceutical-composition comprising (a) pipamperon, and (b) a glucocorticoid synthesis inhibitor, preferably metyrapone or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

End -100 D 01

5

10

15

25

30

35

10

15

20

25

30

35

76

emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

#### 39: combination therapy with a glutamate receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a glutamate receptor antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glutamate receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glutamate receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glutamate receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glutamate receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

r.... . 100 D 01€

F \_ ( ...01 /10 /000 / 00+00

10

15

20

77

According to a preferred embodiment, the invention relates to the uses as described above, wherein said glutamate receptor antagonist compound is LY354740 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a glutamate receptor antagonist, preferably LY354740 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

#### 40: combination therapy with an GPCR (G-protein-coupled receptor) modulator

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an GPCR (G-protein-coupled receptor) modulator, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

25

30

35

-- -- -- ----

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GPCR modulator compound to augment the therapeutic effect or to provide a faster

10

20

25

30

35

78

onset of the therapeutic effect of said GPCR modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GPCR modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GPCR modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said GPCR modulator compound is R1204 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GPCR modulator, preferably R1204 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

#### 41: combination therapy with an GR (glucocorticoid receptor) antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an GR (glucocorticoid receptor) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment

10

15

30

79

disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
  - According to a preferred embodiment, the invention relates to the use as described above, wherein said GR antagonist compound is chosen from the group consisting of ORG 34517/34850 and mifepristone, preferably mifepristone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, mifepristone is to be administered in a daily dose of between 600 and 1200 mg of the active ingredient.
- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GR antagonist, preferably chosen from the group consisting of ORG

10

15

20

25

30

35

34517/34850 and mifepristone, preferably mifepristone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders. premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GR antagonist is Mifepristone, preferably provided in a unitary dose of between 600 and 1200 mg of the active ingredient.

#### 42: combination therapy with a histamine H3-receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a histamine H3-receptor antagonist, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementiadue to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying. emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized

10

15

20

81

in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a histamine H3-receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said histamine H3-receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said histamine H3-receptor antagonist compound is chosen from the group of compounds consisting of ABT-834 and ABT-239, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a histamine H3-receptor antagonist, preferably chosen from the group consisting of ABT-834 and ABT-239 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

25

30

35

#### 43: combination therapy with a hormonal substance

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a hormonal substance, are chosen from the group of diseases or disorders consisting of premenstrual syndrome and sexual and general disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of premenstrual syndrome and sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable

10

15

20

25

salt thereof is administered simultaneously with, separate from or prior to the administration of a hormonal substance to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said hormonal substance, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said hormonal substance is chosen from the group consisting of a testosterone transdermal spray, a testosterone gel, a female testosterone patch, synthetic conjugated estrogen A, methyltestosterone, a estrogens/methyltestosterone and a drosiperone/ethinyl estradiol composition, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said hormonal substance is synthetic conjugated estrogen A and is to be administered in a daily dose ranging between 0.075 and 0.6 mg of the active ingredient. More preferably, said hormonal substance is a drosiperone/ethinyl estradiol composition and is to be administered as a daily dose in tablets, preferably comprising 3mg drosiperone and 0.02 mg ethinyl estradiol of the active ingredients, respectively.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,

- (b) a hormonal substance, preferably chosen from the group consisting of a testosterone transdermal spray, a testosterone gel, a fernale testosterone patch, synthetic conjugated estrogen A, methyltestosterone, a estrogens/methyltestosterone and a drosiperone/ethinyl estradiol composition, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of premenstrual syndrome and sexual and gender identity disorders.
- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said hormonal substance is synthetic conjugated estrogen A, preferably provided in a unitary dose of between 0.075 and 0.6 mg of the active ingredient.
- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient

and wherein said hormonal substance is a drosiperone/ethinyl estradiol composition, preferably provided in tablets comprising a unitary dose of 3mg drosiperone and 0.02 mg ethinyl estradiol of the active ingredients, respectively.

44: combination therapy with a compound which increases brain concentrations of 5-HT The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which increases brain concentrations of 5-HT (serotonin), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders. eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substancerelated disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

15

20

25

30

35

10

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders). factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases brain concentrations of 5-HT (serotonin), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable sait thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to

augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases brain concentrations of 5-HT (serotonin), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

10

15

20

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which increases brain concentrations of 5-HT (serotonin) is chosen from the group consisting of triptosine, tramadol, SP 186, PMD 145 and KW 6055, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which increases brain concentrations of 5-HT (serotonin), preferably chosen from the group consisting of triptosine, tramadol, SP 186, PMD 145 and KW 6055, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

## 25 45: combination therapy with a compound which increases insulin sensitivity

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which increases insulin sensitivity, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

35

30

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases insulin sensitivity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases Insulin sensitivity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which increases insulin sensitivity is rosiglitazone maleate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable sait thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which increases insulin sensitivity, preferably rosiglitazone maleate or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

46: combination therapy with a compound inhibiting the mixed lineage kinase family

The mental disorder which can be treated using compounds having a high selective
affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy

5

10

15

20

25

30

35

10

15

20

30

35

8

with a compound which is an inhibitor of the mixed lineage kinase family is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is an inhibitor of the mixed lineage kinase family to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is an inhibitor of the mixed lineage kinase family, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which is an inhibitor of the mixed lineage kinase family is CEP-1347 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is an inhibitor of the mixed lineage kinase family, preferably CEP-1347 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

25 47: combination therapy with an interleukin-1 beta converting enzyme inhibitor compound
The mental disorder which can be treated using compounds having a high selective
affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
with an interleukin-1 beta converting enzyme inhibitor compound, is a pain disorder.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an interleukin-1 beta converting enzyme inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said interleukin-1 beta converting enzyme inhibitor compound, further

\_ ii

10

20

25

30

35

87

characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said interleukin-1 beta converting enzyme inhibitor is pralnacasan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable sait thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an interleukin-1 beta converting enzyme inhibitor, preferably pralnacasan or a prodrug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a pain disorder,.

#### 48: combination therapy with a levodopa/decarboylase inhibitor compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a levodopa/decarboylase inhibitor compound, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a levodopa/decarboylase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said levodopa/decarboylase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said levodopa/decarboyfase inhibītor compound is levodopa/carbidopa, levodopa/ benserazide, etilevodopa/carbidopa or etilevodopa/benserazide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. According to a further preferred embodiment, the invention relates to the use as described above, wherein said levodopa/decarboylase inhibitor compound is (eti)levodopa/carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-

10

15

20

25

30

35

drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably said levodopa/decarboylase inhibitor compound is levodopa/carbidopa and is to be administered in a dose ranging between 2000 mg/ 50 mg and 100 mg/ 10 mg of the active ingredients. Preferably said entacapone is to be administered in a dose ranging between 1000 mg/ 50 mg, more preferably between 500 mg/ 100 mg, and most preferably 200 mg of the active ingredients per day.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. and (b) a levodopa/decarboylase inhibitor compound, preferably levodopa/carbidopa. levodopa/ benserazide, etilevodopa/carbidopa or etilevodopa/benserazide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease. The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboylase inhibitor compound, preferably is (eti)levodopa/carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboylase inhibitor compound is levodopa/carbidopa, preferably provided in a unitary dose of between 100 mg and 10 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboylase inhibitor compound is levodopa/carbidopa or etilevodopa/ carbidopa in combination with entacapone, of which the latter is preferably provided in a unitary dose of between 500 mg and 100 mg of the active ingredient.

#### 49: combination therapy with a lipid-DNA complex

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a lipid-DNA complex, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of lipid-DNA complex to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said lipid-DNA complex, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

5

According to a preferred embodiment, the invention relates to the use as described above, wherein said lipid-DNA complex is GR213487B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a lipid-DNA complex, preferably GR213487B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

20

25

30

35

#### 50: combination therapy with a monoamine oxidase (MAO) reuptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase (MAO) reuptake inhibitor, are chosen from the group of diseases or disorders consisting of substance related disorders and attention-deficit disorders (ADHD).

The present invention thus relates to the use of plpamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of non-cognitive mental disease or disorder which are substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that

10

15

20

25

30

35

. . - A1 /1A /AAA A AA-AA

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention-deficit disorders (ADHD), characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase (MAO) reuptake inhibitor compound is NS 2359 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase (MAO) reuptake inhibitor, preferably NS 2359 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of substance related disorders and attention-deficit disorders (ADHD).

#### 51: combination therapy with a MAO-A and a MAO-B reuptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor, wherein said disorders are attention-deficit disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention-deficit disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with,

10

15

20

25

30

35

91

separate from or prior to the administration of a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound is SPD473 or a pro-drug or an active metabolite thereof, or a pharma-ceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor, preferably SPD473 or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of attention-deficit disorders.

#### 52: combination therapy with a monoamine oxidase B (MAO-B) inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase B (MAO-B) inhibitor, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, characterized in that pipamperon or said

;+3292802345

5

10

15

20

25

30

35

pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase B (MAO-B) inhibitor compound is chosen from the group consisting of selegiline, rasagiline (TVP-1012) and EmSam (transdermal selegiline), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said monoamine oxidase B (MAO-B) inhibitor is selegiline and is to be administered in a daily dose ranging between 5 and 10 mg of the active ingredient. More preferably, said monoamine oxidase B (MAO-B) inhibitor is rasagiline (TVP-1012) and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient.

10

15

20

25

30

35

93

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase B (MAO-B) inhibitor, preferably chosen from the group consisting of selegiline, rasagiline (TVP-1012) and EmSam (transdermal selegiline), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said monoamine oxidase B (MAO-B) inhibitor is selegiline, preferably provided in a unitary dose of between 5 and 10 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said monoamine oxidase B (MAO-B) inhibitor is rasagiline (TVP-1012), preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

53: combination therapy with a monoamine oxidase B (MAO-B) reuptake inhibitor

The mental disorder which can be treated using compounds having a high selective

affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase B (MAO-B) reuptake inhibitor, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt—thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) reuptake inhibitor to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) reuptake inhibitor, further characterized in that

10

35

1 -- 01 /10 /0004 00+00

94

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above. wherein said monoamine oxidase B (MAO-B) reuptake inhibitor is safinamide or a prodrug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. and (b) a monoamine oxidase B (MAO-B) reuptake inhibitor, preferably safinamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

#### 54: combination therapy with a melanocortin-4 (MC4) receptor antagonist compound

15 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melanocortin-4 (MC4) receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, 20 adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), 30 factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanocortin-4 (MC4) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanocortin-4 (MC4) receptor

٠,

antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanocortin-4 (MC4) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanocortin-4 (MC4) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melanocortin-4 (MC4) receptor antagonist compound is MCL0129, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melanocortin-4 (MC4) receptor antagonist compound, preferably iMCL0129 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

## 30 55: combination therapy with a MCH receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melanin concentrating hormone (MCH) receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity

- i, -774 D 04

Fmof 701/10/2001 27:32

10

15

20

25

35

disorders, sleep disorders, adjustment disorders, impulse control disorders, substancerelated disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanin concentrating hormone (MCH) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanin concentrating hormone (MCH) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20

25

5

10

15

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanin concentrating hormone (MCH) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanin concentrating hormone (MCH) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melanin concentrating hormone (MCH) receptor antagonist compound is SNAP-7941 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

35

15

20

25

30

35

97

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melanin concentrating hormone (MCH) receptor antagonist compound, preferably SNAP-7941 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

#### 56: combination therapy with a melatonin receptor (MT) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melatonin receptor (MT) agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist

compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melatonin receptor (MT) agonist compound is chosen from the group consisting of ramelteon and agomelatine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said melatonin receptor (MT) agonist compound is agomelatine and is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

20

25

30

35

5

10

15

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melatonin receptor (MT) agonist compound, preferably ramelteon or agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said melatonin receptor (MT) agonist compound is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

10

15

20

25

30

35

# 57: combination therapy with a metabotropic glutamate receptor (MgluR) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a metabotropic glutamate receptor (MgluR) agonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a metabotropic glutamate receptor (MgluR) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said metabotropic glutamate receptor (MgluR) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a metabotropic glutamate receptor (MgluR) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said metabotropic glutamate receptor (MgluR) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

25

30

35

According to a preferred embodiment, the invention relates to the uses as described above, wherein said metabotropic glutamate receptor (MgluR) agonist compound is PRE703 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a metabotropic glutamate receptor (MgluR) agonist, preferably PRE703 or a prodrug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

# 58: combination therapy with a compound mimicking the effect of nerve growth factor (NGF)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which mimics the effect of nerve growth factor (NGF), are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20

25

30

35

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which mimics the effect of nerve growth factor (NGF) is xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said compound which mimics the effect of nerve growth factor (NGF) is xaliproden and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which mimics the effect of nerve growth factor (NGF), preferably xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound which mimics the effect of nerve growth factor (NGF) is xaliproden, preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

10

15

20

25

30

35

5

118U21-10-04;22:34

#### 59: combination therapy with a muscarinic receptor partial agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a muscarinic receptor partial agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a muscarinic receptor partial agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said muscarinic receptor partial agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said muscarinic receptor partial agonist compound is sevimeline or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

5

10

15

30

35

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a muscarinic receptor partial agonist compound, preferably sevimeline or a prodrug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

# 60: combination therapy with a selective nor-adrenaline re-uptake inhibitor (NARI) compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective nor-adrenaline re-uptake inhibitor (NARI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or sald pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline receptor inhibitor (NARI) compound to augment the therapeutic

effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline re-uptake inhibitor (NARI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

20

25

35

10

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is chosen from the group consisting of reboxetine, atomoxetine hydrochloride, A 75200. 155U88. (S)-A 75200, tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine and milnacipran or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof: More preferably, said selective nor-adrenaline re-uptake inhibitor (NARI) compound is reboxetine and is to be administered in a daily dose ranging between 8 and 12 mg of the active ingredient. More preferably, said selective nor-adrenaline re-uptake inhibitor (NARI) compound is atomoxetine hydrochloride and is to be administered in a daily dose ranging between 40 and 100 mg of the active ingredient.

30

and (b) a selective nor-adrenaline re-uptake inhibitor (NARI) compound, preferably chosen from the group consisting of reboxetine, atomoxetine hydrochloride, A 75200. 155U88, (S)-A 75200, tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine and milnacipran, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,

disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

5

10

15

20

25

30

35

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline re-uptake Inhibitor (NARI) compound is reboxetine, preferably provided in a unitary dose of between 8 and 12 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is atomoxetine hydrochloride, preferably provided in a unitary dose of between 40 and 100 mg of the active ingredient.

#### 61: combination therapy with a NaSSA compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a noradrenergic/specific serotonergic antidepressant (NaSSA) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse

10

15

20

25

30

or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said noradrenergic/specific serotonergic antidepressant (NaSSA) compound is ORG 4420 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a noradrenergic/specific serotonergic antidepressant (NaSSA) compound, preferably ORG 4420 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

· · - A / 1 / 1000 4 00 0 41

#### 62: combination therapy with a selective NDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor

(NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active Ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease. dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or sald pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective noradrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20

25

٠.

**30** 

35

1 . . . A 11A 1000 1 00 - 11

5

10

15

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162 and is to be administered in a daily dose ranging between 20 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, preferably GW353162 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia,

eu21-10-04;22:32

5

10

15

20

25

30

vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162, preferably provided in a unitary dose of between 20 and 60 mg of the active Ingredient.

#### 63: combination therapy with a compound which is a neuroimmunophilin ligand

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is a neuroimmunophilin ligand, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or-prior to the administration of a compound which is a neuroimmunophilin ligand to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a neuroimmunophilin ligand, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said a compound which is a neuroimmunophilin ligand is GPI.1485 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable sait thereof. More preferably, said a compound which is a neuroimmunophilin ligand is GPI 1485 and is to be administered in a daily dose ranging between 200 and 1000 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a neuroimmunophilin ligand, preferably GPI 1485 or a pro-

drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said a compound which is a neuroimmunophilin ligand is GPI 1485, preferably provided in a unitary dose of between 200 and 1000 mg of the active ingredient.

10

#### 64: combination therapy with a neuromodulator compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neuromodulator compound, is Parkinson Disease.

15

20

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neuromodulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neuromodulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said neuromodulator compound is adenosine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable sait thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neuromodulator compound, preferably adenosine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

## 65: combination therapy with a neurotensin receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurotensin receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders. dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to

5

10

15

20

be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said neurotensin receptor antagonist compound is SR 48692 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurotensin receptor antagonist compound is SR 48692 and is to be administered in a daily dose ranging between 90 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurotensin receptor antagonist compound, preferably SR 48692 or a pro-drug or an active metabolite thereof, or a -pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurotensin receptor antagonist compound is SR 48692, preferably provided in a unitary dose of between 90 and 300 mg of the active ingredient.

5

10

15

# 66: combination therapy with nerve growth factor (NGF) gene therapy

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with nerve growth factor (NGF) gene therapy, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

35

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound useful in nerve growth factor (NGF) gene therapy, preferably xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

It should be understood that "nerve growth factor gene therapy" is well known in the art, and the compounds, for instance nucleic acids used in nerve growth factor gene therapy are well described (see e.g. Tuszynski et al., (2002) Journal of Molecular Neuroscience Volume 19, Issue 1-2, pps. 207-208).

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a nicotinic acetylcholine receptor antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

10

15

20

25

30

35

115

administered simultaneously with, separate from or prior to the administration of a nicotinic acetylcholine receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic acetylcholine receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic acetylcholine receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic acetylcholine receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said nicotinic acetylcholine receptor antagonist compound is SEP174559 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a nicotinic acetylcholine receptor antagonist compound, preferably SEP174559 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

## 68: combination therapy with a nicotinic receptor agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a nicotinic receptor agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia.

vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said nicotinic receptor agonist compound is ABT-089, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said nicotinic receptor agonist compound is ABT-089 and is to be administered in a dally dose ranging between 4 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a nicotinic receptor agonist compound, preferably ABT-089 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Pick Disease,

dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above, wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said nicotinic receptor agonist compound is ABT-089, preferably provided in a unitary dose of between 4 and 40 mg of the active ingredient.

# 10 69: combination therapy with a neurokinin 2 receptor (NK2) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurokinin 2 receptor (NK2) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

20

25

30

15

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personallty disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

25

5

According to a preferred embodiment, the invention relates to the uses as described above, wherein said neurokinin 2 receptor (NK2) antagonist compound is saredutant or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurokinin 2 receptor (NK2) antagonist compound is saredutant and is to be administered in a daily dose ranging between 25 and 200 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurokinin 2 receptor (NK2) antagonist compound, preferably saredutant or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurokinin 2 receptor (NK2) antagonist compound is saredutant, preferably provided in a unitary dose of between 25 and 200 mg of the active ingredient.

10

15

20

25

# 70: combination therapy with a neurokinin 3 receptor (NK3) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurokinin 3 receptor (NK3) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that

٠÷. .

10

15

20

25

30

35

120

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said neurokinin 3 receptor (NK3) antagonist compound is talnetant or osanetant, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurokinin 3 receptor (NK3) antagonist compound is talnetant and is to be administered in a daily dose ranging between 1.5 and 12 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurokinin 3 receptor (NK3) antagonist compound, preferably talnetant or osanetant, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient

10

15

121

and wherein said neurokinin 3 receptor (NK3) antagonist compound is talnetant, preferably provided in a unitary dose of between 1.5 and 12 mg of the active ingredient.

# 71: combination therapy with an N-Methyl-D-aspartate (NMDA) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an N-Methyl-D-aspartate (NMDA) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically 20 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, 25 adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-Daspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a 30 faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that plpamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

10

15

20

35

emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound; further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said N-Methyl-D-aspartate (NMDA) antagonist compound is chosen from the group consisting of SEP174559, memantine, delucemine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said N-Methyl-D-aspartate (NMDA) antagonist compound is memantine and is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an N-Methyl-D-aspartate (NMDA) antagonist compound, preferably chosen from the group consisting of SEP174559, memantine, delucemine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

10

15

20

25

30

35

emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said N-Methyl-D-aspartate (NMDA) antagonist compound is memantine, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

### 72: combination therapy with a non-steroidal anti-inflammatory drug

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a non-steroidal anti-inflammatory drug, is a pain disorder or Alzheimer Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a non-steroidal anti-inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disease, such as Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered

E-nf - ..... 110 10001 00.00

- / -40/ 0 000

simultaneously with, separate from or prior to the administration of a non-steroidal antiinflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said a non-steroidal anti-inflammatory drug is chosen from the group consisting of piroxicam, MX-1094, meloxicam and flurizan (pure R-enantiomer form of flurbiprofen), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. (b) a non-steroidal anti-inflammatory drug, preferably chosen from the group consisting of piroxicam, MX-1094, meloxicam and flurizan (pure R-enantiomer form of flurbiprofen), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a pain disorder or Alzheimer Disease.

20

15

5

10

#### 73: combination therapy with an opoid antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for Instance pipamperon, in a combination therapy with an opoid antagonist compound, are substance related disorders.

25

30

35

It will be appreciated that the terms "opoid" and "opioid" may be used interchangeably.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a opoid antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said opoid antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active Ingredient.

According to a preferred embodiment, the invention relates to the use as described above. wherein sald opoid antagonist compound is naltrexone, preferably as a depot formulation. more preferably in the form of microcapsules, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, said naltrexone is to be administered in the form of a depot, preferably a depot of microcapsules comprising a daily dose of between 192 and 384 mg.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a opoid antagonist, preferably naltrexone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of substance related disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said opoid antagonist compound is naltrexone, preferably provided in a unitary dose of between 192 and 384 mg of the active ingredient.

### 74: combination therapy with an opoid agonist compound

20 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an opoid agonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, 25 dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substancerelated disorders, personality disorders, bereavement, occupational problem and

1. - 64 440 70004 00000

21-10-04;20:22 ;DCB

5

10

15

30

10

15

20

25

30

35

126

problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an opoid agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said opoid agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said opoid agonist compound is chosen from the group consisting of siramesine, E-5842 and cyclazocine, preferably siramesine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an opoid agonist compound, preferably chosen from the group consisting of siramesine, E-5842 and cyclazocine, preferably siramesine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

#### 75: combination therapy with a phosphodiesterase-4 (PDE4) inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a phosphodiesterase-4 (PDE4) inhibitor compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob

Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

- The present invention thus relates to the use of pipamperon or a pharmaceutically 5 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, 10 adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset 15 of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound d to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

Fmpf >~:+001/10/000/ 20000

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- According to a preferred embodiment, the invention relates to the uses as described above, wherein said phosphodiesterase-4 (PDE4) inhibitor compound is chosen from the group consisting of ND1251 and MEM 1917 (R1497), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, 15 and (b) a phosphodiesterase-4 (PDE4) inhibitor antagonist compound, preferably chosen from the group consisting of ND1251 and MEM 1917 (R1497), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group 20 consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting 25 dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders. 30

# 76: combination therapy with a peptidic compound

35

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a peptidic compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome,

somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

10

15

20

35

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is-administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is-to-be-administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group

F== ( 1...01/10/00/1 00\*00

10

15

20

25

30

35

130

of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said peptidic compound is chosen from the group consisting of secretin, PT-141, INN 00835 and beta sheet breaker peptide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said peptidic compound is secretin and is to be administered in a daily dose ranging between 0.2 and 0.4 mg/kg of the active ingredient. More preferably, said peptidic compound is INN 00835 and is to be administered in a daily dose ranging between 18 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a peptidic compound, preferably chosen from the group consisting of secretin, PT-141, INN 00835 and beta sheet breaker peptide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition,

10

15

20

131

substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said peptidic compound is secretin, preferably provided in a unitary dose of 0.2 and 0.4 mg/kg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said peptidic compound is INN 00835, preferably provided in a unitary dose of 18 and 160 mg of the active ingredient.

## 77: combination therapy with a phospholipase A2 inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a phospholipase A2 inhibitor compound which has caspase inhibitor activity, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

25

30

35

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect,, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the

10

15

20

25

30

35

administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phospholipase A2-inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said phospholipase A2 inhibitor compound which has caspase inhibitor activity is chosen from the group consisting of LAX-101a, LAX-101b and LAX-101c, preferably LAX-101a, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a phospholipase A2 inhibitor compound which has caspase inhibitor activity, preferably chosen from the group consisting of LAX-101a, LAX-101b and LAX-101c, more

10

15

20

25

30

35

preferably LAX-101a, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

#### 78: combination therapy with a compound which is a prodrug of uridine

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is a prodrug of uridine, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a prodrug of uridine to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a prodrug of uridine, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

Empf -- : 1 = 0.1 /10 /000/4 00 = 00

EPO MUNCHON

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a prodrug of undine to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a prodrug of uridine, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

5

21-10-04;20:22

: DCB

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which is a prodrug of uridine is RG2133 (triacetyluridine) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

15

20

25

30

35

The invention also relates to a pharmaceutical composition comprising (a) pipamperon. and (b) a compound which is a prodrug of uridine, preferably RG2133 (triacetyluridine) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

# 79: combination therapy with prostaglandin E1 compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with prostaglandin E1 compound, are sexual and gender identity disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate

from or prior to the administration of a prostaglandin E1 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said prostaglandin E1 compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said prostaglandin E1 is alprostadil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said prostaglandin E1 compound is alprostadil, preferably in the form of cream or gel, preferably a topical gel, and is to be administered in a daily dose ranging between 50 and 300 microgram per application of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a prostaglandin E1 compound, preferably alprostadil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of sexual and gender identity disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active Ingredient and wherein said prostaglandin E1 compound is alprostadil, preferably provided in the form of a cream or gel, preferably a topical gel, wherein a unitary dose comprises between 50 and 300 microgram of the active ingredient per application.

# 80: combination therapy with a compound protecting dopaminergic and cholinergic neurons

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which protects dopaminergic and cholinergic neurons, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic

5

10

15

20

25

30

disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20

5

10

15

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

25

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which protects dopaminergic and cholinergic neurons is SR 57667 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

10

137

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which protects dopaminergic and cholinergic neurons, preferably SR 57667 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

#### 81: combination therapy with a psychostimulant

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a psychostimulant, are chosen from the group of diseases or disorders consisting of sleep disorders, attention-deficit disorders and substance-related disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of sleep disorders, attention-deficit disorders and substance-related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a psychostimulant to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said psychostimulant, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

35

Empl - : : : 001 110 10001 0001

According to a preferred embodiment, the invention relates to the uses as described above, wherein said psychostimulant is chosen from the group consisting of SPD 503, r-modafinil and modafinil, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said psychostimulant is SPE 503, more preferably said psychostimulant is modafinil and is to be administered in a daily dose ranging between 200 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a psychostimulant, preferably chosen from the group consisting of SPD 503, r-modafinil and modafinil, more preferably said SPC 503 or modafinil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of sleep disorders, attention-deficit disorders and substance-related disorders.

10

5

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said psychostimulant is modafinil, preferably provided in a unitary dose of between 200 and 600 mg of the active ingredient.

15

20

25

30

35

# 82: combination therapy with a compound which is a Reversible Inhibitor of Mono-Amine oxydase A (RIMA)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding-pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

- / ±104 D 010

10

15

139

administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of monoamine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is chosen from the group consisting of toloxatone, RS 8359, moclobemide, cimoxatone, caroxazone (F.I 6654) and befloxatone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is befloxatone and is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient.

25

30

35

20

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), preferably chosen from the group consisting of toloxatone, RS 8359, moclobemide, cimoxatone, caroxazone (F.I 6654) and befloxatone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, personality and gender identity disorders, adjustment disorders, impulse control disorders, personality

disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is befloxatone, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

# 10 83: combination therapy with a compound which modulates SCT-11

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which modulates SCT-11 (i.e. SCT-11 is a G protein-coupled receptor), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

20

25

15

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which modulates SCT-11 to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which modulates SCT-11, further characterized in that pipamperon is to be administered to a patient in a dally dose ranging between 5 and 15 mg of the active ingredient.

35

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which modulates SCT-11 to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which modulates SCT-11, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

5

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which modulates SCT-11 is SNEC-2 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which modulates SCT-11, preferably SNE-2 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

25

30

35

# 84: combination therapy with a serotonin/dopamine antagonist compound (SDA)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a serotonin/dopamine antagonist compound (SDA), are chosen from the group of diseases or disorders consisting of mccd disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

ľ

Empt -- : : : 01 /10 /000 4 00 : 00

10

15

20

25

30

35

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders. dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders. pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound,

= / -104 D 000

;+3292802345

further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said serotonin/dopamine antagonist compound is chosen from the group consisting of zotepine, ziprasidone, SM-13496, SL 91.0177, sertindole, S-18327, risperidone, quetiapine fumarate (preferably sustained release formulation), quetiapine fumarate (preferably granules), quetiapine, perospirone, paliperidone, olanzapine, ocaperidone, LU 31-131, iloperidone, clozapine, BSF-190555, blonanserin, bifeprunox, asenapine and aripiprazole, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said serotonin/dopamine antagonist compound is chosen from the group consisting of SL 91.0177, sertindole, perospirone, paliperidone, blonanserin, bifeprunox and asenapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said serotonin/dopamine antagonist compound is sertindole and is to be administered in a daily dose ranging between 12 and 24 mg of the active ingredient. More preferably, said serotonin/dopamine antagonist compound is paliperidone and is to be administered in a daily dose ranging between 3 and 15 mg of the active ingredient. More preferably, said serotonin/dopamine antagonist compound is asenapine and is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a serotonin/dopamine antagonist compound, preferably chosen from the group consisting of SL 91.0177, sertindole, perospirone, paliperidone, blonanserin, bifeprunox and asenapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

11-04-140-1000A-00+00

21-10-04:20:22 :DCB

5

10

15

20

25

30

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is sertindole, preferably provided in a unitary dose of between 12 and 24 mg of the active ingredient.

5

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is paliperidone, preferably provided in a unitary dose of between 3 and 15 mg of the active ingredient.

. \_ 10-

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is asenapine, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

15

20

25

#### 85: combination therapy with a selective SDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin and dopamine re-uptake inhibitor (SDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders; dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

30

35

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),

10

15

20

25

30

35

:+3292802345

factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptakeinhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be

10

15

20

146

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin and dopamine reuptake inhibitor (SDRI) compound is bazinaprine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin and dopamine reuptake inhibitor (SDRI) compound, preferably bazinaprine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

25

...

30

35

#### 86: combination therapy with a second messenger beta agonist compound

The mental disorders which can be treated using compounds having a high-selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a second messenger beta agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

20

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25

30

According to a preferred embodiment, the invention relates to the uses as described above, wherein said second messenger beta agonist compound is chosen from the group consisting of SR 57227, rolipram and eplivanserin, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said second messenger beta agonist compound is roliped is to be administered in a daily dose ranging between 1.5 and 3 mg of the active ingredient.

35

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a second messenger beta agonist compound, preferably chosen from the group consisting of SR 57227, rolipram and eplivanserin or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for

10

15

20

simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said second messenger beta agonist compound is rolipram, preferably provided in a unitary dose of between 1.5 and 3 mg of the active ingredient.

#### 87: combination therapy with a secretin pancreatic hormone

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a secretin pancreatic hormone, are chosen from the group of diseases or disorders consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

25

30

35

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the

administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said secretin pancreatic hormone is RG1068 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable sait thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a secretin pancreatic hormone, preferably RG1068, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive

10

15

20

25

30

35

behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

88: combination therapy with a sigma receptor agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a sigma receptor agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor agonist compound to augment the

E-nf nr +10/1 D 1720

30

35

therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- According to a preferred embodiment, the invention relates to the uses as described above, wherein said sigma receptor agonist compound is VPI-013 (also known as OPC-14523) or PRX-00023, preferably VPI-013 (also known as OPC-14523), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sigma receptor agonist compound, preferably VPI-013 (also known as OPC-14523) or PRX-00023, preferably VPI-013 (also known as OPC-14523), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

## 89: combination therapy with a sigma receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a sigma receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the

:+3292802345

5

10

15

20

25

30

35

group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect,, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said sigma receptor antagonist compound is chosen from the group consisting of SR 31742 and EMD 68843, or a pro-drug or an active metabolite thereof, or

•

:+3292602345

a pharmaceutically acceptable salt thereof. More preferably, said sigma receptor antagonist compound is EMD 68843 and is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, 5 and (b) a sigma receptor antagonist compound, preferably chosen from the group consisting of SR 31742 and EMD 68843, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substancerelated disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said sigma receptor antagonist compound is EMD 68843, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

# 90: combination therapy with a selective SNDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious-disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition,

10

15

20

25

30

35

substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt-thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20

25

30

35

5

10

15

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 1.5 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to

15

20

25

30

35

· · - 0 · / 10 / 1000 4 00 0 4E

head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound is selected from the group consisting of NS 2330; McN 5652; DOV 216,303 and DOV 21,947; more preferably NS 2330 or DOV 216,303; or a pro-drug or an active metabolite thereof; or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, preferably selected from the group consisting of NS 2330; McN 5652; DOV 216,303 and DOV 21,947, more preferably NS 2330 or DOV 216,303, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attentiondeficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

EPO Munchen

5

10

15

20

25

30

35

.. :

156

#### 91: combination therapy with a selective SNRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor

10

15

20

25

30

35

157

(SNRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is selected from the group consisting of venlafaxine, tomoxetine, tandamine. talsupram, talopram, nefazodone, milnacipran, LY 113.821, duloxetine, desvenlafaxine and amoxapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is chosen from the group consisting of ventafaxine. tomoxetine, milnacipran, duloxetine and desvenlafaxine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is venlafaxine and is to be administered in a daily dose ranging between 75 and 300 mg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is tomoxetine and is to be administered in a daily dose ranging between 0.475 and 3.8 mg/kg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is milnacipran and is to be administered in a daily dose ranging between 50 and 200 mg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is duloxetine and is to be administered in a daily dose ranging between 40 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, preferably selected from the group consisting of venlafaxine, tomoxetine, tandamine, talsupram, talopram, nefazodone, milnacipran, LY 113.821, duloxetine, desvenlafaxine and amoxapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

10

15

25

30

35

EPO Munchen

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is venlafaxine, preferably provided in a unitary dose of between between 75 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is tomoxetine, preferably provided in a unitary dose of between 0.475 and 3.8 mg/kg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is milnacipran, preferably provided in a unitary dose of between 50 and 200 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein 20 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is duloxetine, preferably provided in a unitary dose of between 40 and 60 mg of the active ingredient.

## 92: combination therapy with a selective serotonin re-uptake inhibitor (SSRI) compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin re-uptake inhibitor (SSRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour. bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin re-uptake inhibitor (SSRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

20

10

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin re-uptake inhibitor (SSRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25

30

35

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin re-uptake inhibitor (SSRI) compound is selected from the group consisting of YM 992, VPI-013 (also known as OPC-14523), sertraline, paroxetine, LY 214.281, LU AA-21-004, -Lu-35-138, litoxetine, ifoxetine, fluvoxamine (controlled release formulation), fluvoxamine, fluoxetine, femoxetine, escitalopram, EMD 68843, cyanodothepine, citalopram, venlafaxine, mllnacipran, duloxetine, cericlamine and ademethionine (preferably s-adenosylmethionine), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is chosen from the group consisting of litoxetine, fluvoxamine (controlled release formulation) and escitalopram, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

:+3292802345

5

10

15

20

25

30

160

More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is fluvoxamine (controlled release formulation) and is to be administered in a daily dose ranging between 100 and 300 mg of the active ingredient. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is escitalopram and is to be administered in a daily dose ranging between 10 and 20 mg of the active ingredient. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is citalopram and is to be administered in a daily dose ranging between 10 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin re-uptake inhibitor (SSRI) compound, preferably selected from the group consisting of YM 992, VPI-013 (also known as OPC-14523), sertraline, paroxetine, LY 214.281, LU AA 21-004, Lu 35-138, litoxetine, ifoxetine, fluvoxamine (controlled release formulation), fluvoxamine, fluoxetine, femoxetine, escitalopram, EMD 68843, cyanodothepine, citalopram, venlafaxine, milnacipran, duloxetine, cericlamine and ademethionine (preferably s-adenosylmethionine), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is fluvoxamine (controlled release formulation), preferably provided in a unitary dose of between between 100 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is escitalopram, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

..... 110 MOON & ODO 47

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is citalogram, preferably provided in a unitary dose of between 10 and 40 mg of the active ingredient.

5

10

15

20

25

30

Citalopram or citalopram hydrobromide is a selective serotonin (5-hydroxytryptamine / 5-HT) re-uptake inhibitor (SSRI) and is the conventional name given for the compound of the formula (RS)-1-[3-(dimethylamino)propyl]-1-(p-flurophenyl)-5-phthalancarbonitrile-hydro-bromide. According to an embodiment, a daily doses of active ingredient of SSRI, preferably citalopram, ranges between 10 and 40 mg per day. Preferably, daily doses of active ingredient ranging between 20 and 30 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

Fluvoxamine or fluvoxamine maleate (luvox, fevarin) is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2aminoethyl) oxime maleate (1:1).

According to an embodiment, a daily dose of active ingredient of fluvoxamine in a controlled release mode ranges between 100 and 300 mg per day. Preferably, daily doses of active ingredient ranging between 150 and 200 mg per day are administered in a controlled release mode. More preferably, a daily dose of 100, 150, 200, 250 or 300 mg per day is administered by controlled release.

# 93: combination therapy with a substance P receptor (NK1) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a substance P receptor (NK1) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a substance P receptor (NK1) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

20

10

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a substance P receptor (NK1) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25

30

35

According to a preferred embodiment, the invention relates to the uses as described above, wherein said substance P receptor (NK1) antagonist compound is chosen from the group consisting of vestipitant, TAK-637, R673, GW823296, GW679769, GW597599, CP-122.721, aprepitant, 823296 and 679769, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said substance P receptor (NK1) antagonist compound is aprepitant and is to be administered in a daily dose ranging between 40 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a substance P receptor (NK1) antagonist compound, preferably chosen from the group consisting of vestipitant, TAK-637, R673, GW823296, GW679769, GW597599, CP-

15

20

25

30

35

122.721, aprepitant, 823296 and 679769, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said substance P receptor (NK1) antagonist compound is aprepitant, preferably provided in a unitary dose of between 40 and 160 mg of the active ingredient.

# 94: combination therapy with a sulfonamide compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a sulfonamide compound, are chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering,

10

15

20

25

30

35

antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of paln disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said sulfonamide compound is zonisamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said sulfonamide compound is zonisamide and is to be administered in a daily dose ranging between 100 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sulfonamide compound, preferably zonisamide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined

Foot or :670 P.044

20 + CC

preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

10

5

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said sulfonamide compound is zonisamide, preferably provided in a unitary dose of between 100 and 600 mg of the active ingredient.

15

20

25

30

35

# 95: combination therapy with a tachyklnin antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a tachykinin antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of

a tachykinin antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a tachykinin antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said tachykinin antagonist compound is SR 48968 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a tachykinin antagonist compound, preferably SR 48968 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

30

35

20

25

96: combination therapy with a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, are chosen from the group of

EPO Munchen

diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive Impairment disorder, other cognitive disorders and Parkinson Disease.

15

20

25

30

35

10

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, occupational problem, identity problem, phase of life problem, academic problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the group consisting of R228060 (YKP-10A). palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

25

30

35

168

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

# 97: combination therapy with a vasopressin 1B receptor (V1B) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a vasopressin 1B receptor (V1B) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating

15

20

25

30

35

169

disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a vasopressin 1B receptor (V1B) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vasopressin 1B receptor (V1B) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a vasopressin 1B receptor (V1B) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vasopressin 1B receptor (V1B) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said vasopressin 1B receptor (V1B) antagonist compound is SSR149415 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a vasopressin 1B receptor (V1B) antagonist compound, preferably SSR149415 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders,

.. Empf.zeit:21/10/2004 20:49

bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

# 98: combination therapy with a voltage-gated calcium channel α(2)δ subunit modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a voltage-gated calcium channel alpha(2)delta subunit modulator compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

15

20

25

30

35

5

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a voltage-gated calcium channel alpha(2)delta subunit modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said voltage-gated calcium channel alpha(2)delta subunit modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present Invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a voltage-gated calcium channel alpha(2)delta

Empf pr :670 P.050

subunit modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said voltage-gated calcium channel alpha(2)delta subunit modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

10

15

20

According to a preferred embodiment, the invention relates to the uses as described above, wherein said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin or PD-200,390; or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin, and is to be administered in a daily dose ranging between 50 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a voltage-gated calcium channel alpha(2)delta subunit modulator compound, preferably pregabalin or PD-200,390; or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

25

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin, preferably provided in a unitary dose of between 50 and 600 mg of the active ingredient.

30

35

# 99: combination therapy with a vomeropherin compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a vomeropherin compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual

172

and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

- The present invention thus relates to the use of pipamperon or a pharmaceutically 5 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, 10 adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of vomeropherin compound to augment the therapeutic effect or to provide a faster onset of the therapeutic 15 effect of said vomeropherin compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- According to a preferred embodiment, the invention relates to the use as described above, wherein said vomeropherin compound is PH94B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) vomeropherin compound, preferably PH94B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

Also, the invention relates in particular to the use as described before, wherein said second compound is chosen from the group consisting of fluvoxamine controlled release,

hydrochloride. phenserine tartrate. atomoxetine bupropion (controlled-release formulation), ropinirole HCL (controlled-release formulation), INN 00835, galantamine (extended release formulation), paliperidone, tomoxetine, aprepitant, rivastigmine tartrate. ORG 34517/34850, sunepitron, sumanirole, milnacipran, idazoxan, xaliproden, SR 58611. befloxatone, litoxetine, tianeptine, agomelatine, SPD 503, flesinoxan, bifeprunox. ramelteon, etilevodopa, rasagiline (TVP-1012) and desvenlafaxine.

Also, the invention relates in particular to the use as described before, wherein said second compound is chosen from the group consisting of galantamine (extended release formulation), R121919, risperidone, paliperidone and R228060 (YKP-10A).

The disclosure of all patents, publications (including published patent publications), and database accession numbers and depository accession numbers referenced in this specification are specifically incorporated herein by reference in their entirety to the same extent as if each such individual patent, publication, and database accession number, and depository accession number were specifically and individually indicated to be incorporated by reference. 15

The invention, now being generally described, will be more readily understood by reference to the following tables and examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention and are not intended to limit the invention.

D- 14

**EPO Munchen** 

#### Short description of the Tables and Figures

Table 1: In Table 1, the pKi values of test compounds are given for each of the dopamine receptors, 5HT receptors, adrenergic receptors and the histamine1 receptor.

Table 2: Set-up of a clinical trial comprising for treatment groups.

Table 3: Overview of a placebo, active and period controlled clinical trial in a fore-going pipamperon - citalopram treatment in Major Depressive Disorder.

Table 4: POC process for major depressive disorder.

Table 5: Summary of diseases and disorders relative to known psycho-tropics.

Table 6: Overview of Pharmacological grouping, indicating pharmacological profile 15 numbering (column 2), pharmacological profile (column 3), main indication(s) (column 4), name of the compound (column 4), the dose range (column 5), and the company producing or selling said compound (column 6). Compounds indicated by hatching are preferred.

20

5

10

Figure 1: Add-on treatment with pipamperon after treatment with citalogram.

Figure 2: HDRS-17 change from baseline: combo treatment pipamperon as add-on citalopram vs SNRI (duloxetine) in Major Depression.

25

- Figure 3: Remission rates (HDRS-17 <=7): combo treatment pipamperon as add-on citalopram vs SNRI (venlafaxine) vs SSRIs vs placebo in Major Depression.
- Figure 4: Fore-going treatment during 1-5 days with pipamperon followed with the combination treatment of pipamperon and citalopram. 30
  - Figure 5: HDRS-17 change from baseline: combo treatment pipamperon citalopram with a fore-going treatment of 4 days with pipamperon vs SNRI (duloxetine) in Major Depression.

35

Figure 6: Remission rates (HDRS-17 <=7): combo pipamperon - citalopram with a foregoing treatment of 4 days with pipamperon vs SNRI (venlafaxine) in Major Depression.

EPO Munchen

Figure 7: Fore-going treatment during 6-8 days with pipamperon followed with the combination treatment of pipamperon and citalogram.

Figure 8: HDRS-17 change from baseline: combo treatment pipamperon - citalopram with a fore-going treatment of 7 days with pipamperon vs SNRI (duloxetine) in Major Depression.

10

5

Figure 9: Fore-going and add-on treatment with pipamperon in MDD.

Figure 10: HDRS-17 change from baseline: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SNRI duloxetine in Major Depression.

15

Figure 11: Remission rates (HDRS-17 <=7): fore-going and add-on treatment with pipamperon and citalopram in comparison with the SNRI venlafaxine in Major Depression.

Figure 12: Y-BOCS total score: fore-going and add-on treatment with pipamperon and 20 citalopram in comparison with the SSRI fluvoxamine in OCD.

Figure 13: Y-BOCS obsession score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.

Figure 14: Y-BOCS compulsion score: fore-going and add-on treatment with pipamperon 25 and citalopram in comparison with the SSRI fluvoxamine in OCD.

Figure 15: CGI-severity score: fore-going and add-on treatment with pipamperon and citalopram in . comparison with the SSRI in panic disorder.

Table 1

			-		1					$\neg \neg$					$\neg$	T		$\neg$		ृ त		- 1	
TH	6<	6≮	0	68	6<	٥	9	٥	9	6-7	٥	ઉ	0	0	7-8	9	28	٥	9	8.9	0	28	8
Betal	9>	9>	0	9>	8	\$	0		٥	\$	0	ş	0	0	<i>L</i> -9	9	\$	0	٥	\$	9>	Å	8
Betal	8	Ŷ	0	\$	٧	8	9	-	0	\$	0	<6	0	0	6-7	0	8	0	0	\$	9>	8	Ŷ
Alpha2C	7-8	5	168	5.5	8-7	6.7	-	٥	0	6-7	0	9>	0	0	7-8	0	6.8	0	0	6.7	16811	7-8	6-7
<b>Alsadql</b> A	8.	100	68	6-7	7-8	7-8	0	0	0	6-7	0	6.7	0	0	7-8	0	6.8	0	0	7-8	6.8	7-8	7-8
Assiqla	6-8	5	8-9	6-7	7-8	6-7	6-7	8	\$	6-7	9	9	6-7	8	6-7	0	7-8	<b>e</b>	9>	9>	6.8	6-7	6-7
AledqlA	\$3	0	5.5	7-8	6-8	6-8	200	7-8	\$	50	\$	<b>#68</b>	8	Ş	0	認認	Š	6-7	6-7	7-8	6.7	16.87	0
3en <sub>7</sub> Thi	200	0	0	6-7	7-8	7-8	0	0	0	0	0	2-9	0	0	0	0	0	0 .	0	6-7	0	18.6	0
Je13TH2	8	0		7-8	7-8	7-8	0	0	0	0	0	¥	0	-	0	0	0	0	0	0	0	7-8	0
27LHS		-	8		7-8	7-8	6-7	99	Ş	6.8	8-7	A	8.9	8	0	7-8	7-8	7-8	8	6-7	8	168	0
arTHZ	8	-			6.8	8.9	0	0	8	0	-	8	0		-	0	0	1.3	6-7	5	0	1618	0
Yanks		0.0					6.0	6.8		6	200					8	36					0.2	8.9
ailhiè	0	c			6-7	0	0	0	0	29	11121	100	0	0	0	0	8	0		8	0	0	8
SHTIE	7.8	1:	; ; ;	, 8	6.7	0	-	0		13	0	8	-	-	8	0	8	-	-	8	-	5	Ŷ
di THIS	6.8	2.0	2 8	6.7	6.7	0	0	0	\varphi	7.8	0	8	-	-	. 8	0	6.7	13	8	Æ	8.7	6.8	6-7
BILLES	6-8	<u></u>	2 4	7 5	6.7	0	0	0	¥	2,5	-	12	6	,   -	8	0	6.8	5	8	\\$	2	68	6-7
AITHS	6.8		╫	\$ 8	6.7	116.8	2.8	8	2	3 3	8	8	1	<b>1</b>	2 2	8-7	6.3	8	8	13		8.9	9>
	630						8.0					100	1000	P C	0								
D3	6.8	100		9 2		2.5 8.7		1		0.0	7.7			::: ::::	2	6-8 6-8	7-8		7.8	: [	3 4	2,5	
DS	0.5:8			9 2	2 2	, F	2 2	2 2	Т	242	200	194.11 11.92	100	8 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	200	6	0.0	2,2	134	2	3 5		67
IOI	15 15 15 15 15 15 15 15 15 15 15 15 15 1			2 %	╁	+	+.	3 3	; ×	$\neg \vdash$		- 5	77	_	9 0	7	+	+-	Т	7	3 6	該	0
		4	$\dagger$	+	+	$\dagger$	1		1	†	1			1	T	1	T		T			T	
	22		ဥ	OXBI OXBI				, sozide	Animperograms	GGK218231	Sertificacie	20,00	Haioperido:		Kaciopride	Ocaneridone	Rieneridone	אוממוג	35		100	7innocidone	Pipamperon
	CCCSONO		Zotepine	Fluparoxan	Olgazapine	Clean	610207	2010		3 .	Seringole 100		inalo i	Tiospirone	Kacio	ST C	D G	routen	400000	2 0	Seroduci		i g

הבי יפשט ח חבב

FOLLOW-UP	
HASE COLLON HASE  SHASE  SHASE	
HASE HASE HASE HASE HASE HASE HASE HASE	
	111
	計量
	132 132
	732
	572
	<b>K</b>
	111
	疆
	聲
	3
	# U
	A: PLC + PLC
	35
	¥ ×
	T)
	***
	4
<b>1000000000000000000000000000000000000</b>	
	Treatment regimen:
	식음
THE STATE OF THE S	3 I S
	#I <del>=</del>

C: 2x(CIT(10mg)+PIP(4mg))/d

D: 2x(CIT(10mg)+PLC)/d

\*Neuronal E-Clinical Trial = Vesalius Expert Development for this Trial which includes the bottom-up measurement of: \*\*Entering Acute Phase: only NON-placebo responders as defined by the DSM-IV criteria of efficacy

\*\*\*Entering Extension Phase: only remittors as defined by the DSM-IV criteria of efficacy

\*\*\*\*CGI-S: Clinical Global Impressions-Improvement Scale

\*\*\*\*\*Q-LES-Q: Quality of Life, Enjoyment and Satisfaction Questionnaire

171

Table 3

· · · · · · · · · · · · · · · · · · ·	4	100	- 30cc	1		-4		1.7	46.		1.11	100
			2,5	g e	U W	坦		丰丰	312	1	F	13-1
	- 6	<u>0 - ن</u>		<u> </u>	E C	dill the list	×	X		12		×
	8			ن ن	00		2	ΙΞĒ	76		ΕĖ	
	¥			o c	o o			13	7 5	4	T.E.	
	a.			35		===	27 E					
				包含	0.0	=		E		127	1	
	3 1					44		X	ŒĿ		i i	1
	io i					學學	:  - <u>}-</u>	( ×	÷F.	-13		FI
				当員			11 #	11	唱	:1=		鰏
	₩.Ε	222		器医		翼			: 7 2	1	뒢	
	- F		205 L		10.00	-		124	ш	135	== :	副意
	Ĭ	300		<b>3</b> 12				X		Ž X		鲻
		- V. A. G.					====	22.25	= 1		133	
					回运	3	話達		翻		ET.	XX
	Ē		15.75			=					1	
			海岸			141			H.XIII	計		××
	N PHASE ***		793	<b>20</b>		34	9	100	7	24		
4	Z.	VAC The	2.7	<b>E</b>	10	Ė		멸		SK	l'O	XX
	4			芸貞		155					韫	
	≥ .					÷	111	11 2.5		2 2	127	12 2
	욼		233			14		ᆀ꿏		55.5	14	H.X
	3	200	T.				711 4	11 11	1	CE NO.	127	11
	E XTENS!	The contract				· 中国   10   10   10   10   10   10   10   1			閾		أبحا	××
	û		1925	三元	世界			레프	<b>F</b>	15		리트
1		e en de fe	1000			12		1 21			IEI.	XX
						15			闦	重幅		部
		71251259			2111	5		TE IES		#5 <b>#</b> #	131	F (FX: 11X:
			10.00		計器員	Ħ		×××	×	×,	Weight Trx	MX
<b>Carrol</b> Carrol						4 =	133	2.4	177			XX P
			3	凿			誾	TAKE WANTED THAT WANTED THAT THAT THAT THAT THE PARTY OF			12	TXI UX
	ŝ				3 2 3	E 4:	100	3 2	匝	231	141	
Carlo			- 10	德				٠į ج	룺		計劃	××
	₹ '					a F			#:			Ţ
	),	Carlotte To					7	땅	七日			Ž X
						48	됆		177	وابق		II
		19,00				3 1		n= 2:	譜	34.3	三年	댎
0	J.			逻			園	X	淵			XI.
	Şi	1000	22.70						i e	222 12		××
≥	ė.				10		坦	×E:	瞳		罪	XIS
S##10:4:≤	4			1000		2 =		Tab SE		-		
α ≥ c	1							X				
O - F		and a				5			ata ir	74.44	3.	
	増			نخ			閆	FCX III THE			到	
		iba ya		9	2	<u> </u>	<b>#</b> -	<b>FIR</b>	45	H	1.	l#fi
0 0	-3	200				氢氯	11		144		-  :=	L F
				<u>;</u> ⊑;		골길			框			
≲ υ	Ã			ΣĦ					浬		貫建	
Z 4	2	N. T.		33		Sľ	5		1		I F	
	75					出			业		- 5	
# - <b>T</b>	2					副			12	Hill	7.7	<b>!!!!</b>
		270		38	星譜		932		3		21#	据记
$\boldsymbol{\sigma}$						喜喜	휘떀		1	圕	틾뉱	
	::	and the sale	1 200	100		. I	1		15	ne i		131
O			五田	2012		#F			1			
				29	<b>学</b> 高		計画			bit	劃	1315
	#F			199		圛:		陆影	4	17.04		
	ψĊ		3	<b>6</b> =			訓導	讄			5d 5	11
C .	# E		<b>3</b>		美型		影響			1	製品	185
0 =	I TE PHASE									백비		X
Heritage 1995	a, E	200	4 22	20		롈		THE	11		<u> </u>	丰丰
	_ ī				坚制	<b>E</b>	40	丰	占		1	19
	<b>∷</b> ¦≤		設設	=57×		의	計画	F. 1			32 5	下上
	_i			보급			G A		4			14
	#E_							-	11-	1=		10
		- 11		当篇	要解	築			些:	博		1
					딸일	살	2920	清	왉	肥		H#F
					13.15	9		鰕	, is	×	灵	
			<b>2</b> 12	- 0	UU				15		器	批批
		- 0	<b>尾門</b>	8 o			運		앀	軍		التزاة
	躝				H		清厚		-11		題牌	1127
						圝	-15	1 1	7	2 125		-1:-1
			劉皇	-344	0.0	畫	1	扫	r:Fit	1	FE	
				3	0	罥	<u>.</u> ]:-	Jjali	먇	414	E341	
	21		治性	O. O	0.0	뾜		闊	등	ş işi	[Zľ	테내
	亩		3 5	5	<b>100</b>		2015	扫	3		[등].	시설
	Ħ	FROS	德屋	15		園	::: C		بان	စွဲပြွ	القا	
		- W	υL.	III d		2	373	اتا	름.	)[교	阌	되임
	鸖	22.2	岩麓			10	:11		햜Η	= -		텔
				40	-0.50	6	# 3	받니	重	:F	輕!	9["I
			多温度	χ.	920	谱		17	<u> </u>	붸뺻	151	14

\*Neuronal E-Clinical Trial = Vesallus Expert Development for this Trial which includes the bottom-up measurament of:

. In- and exclusioncrileria

. Functional status evaluation

. Medical history

(Pre-]trea timent signs & symptoms

. DSM-IV rules for diagnosts & efficacy

. Reting Scales: HDRS-28. MADRS, HAMA

. Medical resource utulisation

. Pre-vital & Concomittant medication

. Drug administration

. Gentuos) Adverse events

. Admission to the acute and extension phase of treatment

. Right flow of the trial

\*\*Entering Extension Phase: only remittons as defined by the DSM-IV criteria of efficacy

\*\*Entering Acute Phase: only NON-placebo responders as defined by the DSM-IV criteria of efficacy

••••C-LES-Q: Quality of Life, Enjoyment and Satisfaction Questionnaire

178

.. . Table 4

DAY	minus D7	D0	=>D4
TREATMENTGROUP			
Placebo (PLC)	PLC+PLC	2x(PLC+PLC)	2x(PLC+PC)
PIP - Active / Day 4	PLC+PLC	2x(PLC+PIP (4mg))/d	2x(CIT (10mg)+PIP (4mg))/d
PIP - Active / Day 0	PLC+PLC	2x(CIT (10mg)+PIP (4mg))/d	2x(CIT (10mg)+PIP (4mg))/d
PLC - Active / Day 0	PLC+PLC	2x(CIT (10mg)+PLC)/d	2x(CIT (10mg)+PLC)/d
ĺ			

LEO MUNCHEN

Table 5

enacumancenellusicsparagodajuanyesojogasi		
	NOW.	constra
	<u>                                     </u>	
	Ariania Ariania	SSRVI SVRITSVORIY SZNIT (NAKTYNOHI) NSSSY (RBAA-1 MAGAY GUNGE) BYTATI SHITIFI SHITIF SHITIGO (64120 64127 64127
MEDICA, INDICATION		
IRDISOPORAWITH AN UKARAHYING EMOTION DYSHERUIATION	×	× × × × × × × × × × × × × × × × × × ×
THIN THO PHECOGNITIVE NEW TAW DISONOENS (GOT PANIS) FOR SAIN	-	
Terrational Labert Called the Health High Laboration of the Control of the Contro		\$ \cdot
Repairing Wilso	×	
orothys lautement		×
(reversion of the control of the con	c'×	
dispetative director	×	\$
sexual and gordes to sexual and gordes to sexual and se	×××	× × × × × × × × × × × × × × × × × × ×
soposo puntanto	×	X 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Supulso control disarders	×	X X X X X X X X X X X X X X X X X X X
pervesty development disorder	×	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
actor property of the control of the	×	
substance-related disadors	×	÷
anothern textored a cocost textored textored	×	ορίτου ορίτου ο την ουτροποία ο αρουία ο προυία ο προυματικό συσματικό που πολουματικό πρού την εξεποία πρού τ 
Bujardujaw	×	- 4 - 2 - 4 - 1 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 4 - 2 - 2
mayanda (abasina	××	**************************************
occupation problem	×	X
melden (forther)	×××	
maldery almost	×	
problems related to chuse or medical	×	
липлинининининининин		X X X X X X X X X X X X X X X X X X X
ARTHAINTHINING CONTINUE TO THE		
dellum		
Azhetner Uterate		, , , , , , , , , , , , , , , , , , ,
Samuel ulasev		×
demantis des lo HiV disease		
demental of the table of the table of the table of table		
dementia due to Hurthgan Otrone		×
demonstage Discuso		
reduction is a few to the to the second of t	×	
substance-induced pentisting annests deorder	×	-
which instruction of the control districts and control districts and control of the control of t	×××	, x,
ANTHUMINININININININININININININININININININ		

Pate & Contract Head on the Principal Parish High High High High High High High Hig															
										Н		H	H	$\prod$	
		CONSO													
	-	SHTZADA-Antegonial ochš samoosn	+CNS compound							l					
								•							
	Antigorisi	1	6HI*teuplche anhance	braces but	Sufratures P Artegorial	Anthoperits	lachyddin sniegosibi	polytical	MCH' enoughs	MI*	Ollecorin	CHIP-1- C	Open, Mea	oratio exertit	things 2
						Н				-	1		_	Ħ	
меиса. Інрісапон										H		H			
albisokoppy with aleukoppublo falotiquo kareoutation	×		×	×	×	×	×	×	×	×	×	×	×	×	×
(12 or 12 or								$\mid$		$\vdash$		$\vdash$	$\vdash$	F	
מיווינונים ארכינים וואם שבעו של הוא המיים של היו היווים של היווים ביווים ביווים ביווים ביווים ביווים ביווים בי		_	,	Å	-	,	ì	-	,	7	order virtue	-	-	Transport.	,
	×		×	×	X		×	35	×				Ç×		C 2C
emparte eguated							-					- 3			×
andra Graden	×		×	×	×	×	×	×	×	×	×	×	`.	×	×
small and and any any and any	×		*	\$	*	×>	×	×	\$\$	×.	×n	×	×	×	X12
sapos pangur	*	Ì	×	×	×	< ×	<b>*</b>		×			. į.	4	*	
disedative Gooden	×		×	×	×	×	×	×	×	×	×	×	×	*	ż
second and gender kinnity decelers	×		×	×	×	×	×	DC		×	200	×	×	-	<b>.</b> ×
singuage decis	×		×	×	×	×	×	×	X	×	×		×	×	×
countries diaden	×		×	×	×	×	×	×.	×	×	×	×	×	×	×
ענייים ביילים לוויילים לוויילים לוויילים:			×	×	X	×	×	×	×	×	×	×	×	Χ.	×
Appropriate the second							-	×	•	-	-	-			-
Caraban describe			•	·	7	*	+	•		÷		÷	-	*	
eufabres-releted Granters	×		×	×	×	×	×	×	×	×	×	- ×	×	×	×
porantly deaders	×		×	×	×	×	×	×	×	×	×	×	×	×	
psychological focus alleging medical conditions	×					-						- \		- 1	
Antiocelal behavior	1		×	P	Ţ	·	-	•		-	,		-		-
bereamen,	×		×	×	×	×	×	×	×	×	X	×	``.	×	×
constraint profess	×		×	×	×	×	×	×	×	×	×	×	×	×	×
Kentity profess	×														
margarita estad										. ;		-		,	
misco to concerns			×	×	×	×	×	×	×	- i-	×	×	×		3
EHITHMINGTONAKANISHIJAMIANGHANISHINGTONAKA		_	×	×	×	×	×	×	×	×	×	- ×	×	×	
AFILITER TO THE THE THE PROPERTY OF THE PROPER									•	1					
Collection										-				-	-
Author Dhouse								×							
יייייייייייייייייייייייייייייייייייייי						-}		~ ;		-		- }	-	-	
establish despuisemb			· · · · · · · · · · · · · · · · · · ·	T	-	*	+	-			· · · · · · · · · ·	÷	-		
dementa de la hand trauma						-	-		-	:	•	-	-		
commits due lo Partinum Cleman								×		-	·	ļ.		-	
concrete due to Haultgan Chans								×		-		-	-	-	
demarks the Part of the Character				,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		,		×						,	
with the family and a second of second	ļ							*		-	-	-!	-	-	-
whatere indued position amounts decrea	×					-	-	÷		÷	Ť	÷	+	-	
mild caprifine impairment classifier	×							×	3 1	-		-			
ether cognitive disorders	×	_				,		×						. ,	
San and the state of the state of the state of the san		-			*******	**			***********		*****				
The same of the sa					-	-	•	-	•	-		-	-	-	

:+3292602345

٠٠٠-

<u> </u>	
	Secreting percental Band Dr. eringodia 'entigra Nur
	cangolist pola antiqo antaga
x	
	> × ×
	×
<pre></pre>	
	X
**************************************	**
**************************************	X 1 2 1 10 1 1 1 1 1 1 1
******** *** ** ** * * * * * * * * * *	
******* *** ** * * * * * * * * * * * *	× - × - × - × - × - × - × - × - × - × -
****** *** *** ** * * * * * * * * * *	
*****	
****	
*** ***	
**	×
* * * * * * * * * * * * * * * * * * *	
××× ×× × × × × × × × × × × × × × × × ×	X X X
***	
**	X - X - X
xxxxxxxx	
xxxxxxx	X X X X X X X X X X X X X X X X X X X
××××××	X X X X X X X X X X X X X X X X X X X
×××××	10 - 1 - 10 - 10 - 10 - 10 - 10 - 10 -
x x x x x x x x x x x x x x x x x x x	1000 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
× × × ×	
×	
X X X X X X X X X X X X X X X X X X X	
	X X X X X X X X X X X X X X X X X X X
	**************************************
,	
_	
х пароприцибраци	
III HTHIRII III III III III III III III III II	

The control of the co											1		l				
Application of the company of the co	Transferration of the contract	- Contract	COMBO														
The company of the co		4	1														
		事のから	Ť	ACNS COTTOOL	P										-	ŀ	
		PHILIDAD C	İ	UPA receptor	L		prostagandn E t	aychos(Imutan)	mphidement	opioid receptor		gicocofeeld synhesis hifther		_		_1	it the the the
		Arapatal	-	medalia									+	1	+	1	
	MEDGALINDICATION													╁,	<u>                                     </u>	}	ľ
	TOPSOFOERWILLIAN UNDERLYPHOER OTIGNOY SPECIULATION	ľ		-	×	×	×	×	×	×	×	T	+	+	+		
		_	_		-	_		-					-	-	-		
	IIIK NOW COCKITIVE MENTAL ISING KING KAN KAN UNING		_	×					J				-				
		×		×							:					-	
	Salar Children and Children and Children and Children			×	-						-					-	
	eating dratter	×		*		-						,		×		-	-
	parametrial syndome	Ž									- 4			-			-
	sanztolom deaches (ochuling Puln Grande)			×	-				-	1	-			-			
	the state of the s	*		×					-	***************************************	1		*****	•	<u>:</u>		
	CONSCIONA GRANTS	,				×	×						•			-	-
	securiard gender loanly assembly	*		×	×			×			:			-			
	acousts does	}		×							1		-				
	Appropriate the second	}		×				-			1		+-	-	:-		-
	and the desired and an arrangement of the state of the st	×		×		-			***				×	-			
	STATE OF THE PROPERTY OF THE P	×						····									
	dunita interior dunitarior	×		×						×	×	×	×	-	-	-	
	substance-réaled diorders	×		*										-	-		
	peratty dunder	×		-	********						- 4						-
	psychological factors affecting medical cardidates	<b>\</b>		×	-						-						
	The state of the s	1		~							*			•	-		
	hadracand .	×		×									·-	-	-		-
	Catholic Control	×		×	-	-							-				
	bashymothen	×		×	-												- ;
	these of its problem	×		-							-		-	-		-	-
	academio prodrem	×		-			-						-	-	-	-	-
	problems refered to abuse or reduce	×	- -,	, ,													
			-	×													
	awiningangananananananananananan		- -						,		1		•				
	Sagagonakinkanikanikanikanikanikanikanikanikan						-	-							-		
	teller			×											×	×	×
	Athebrei Deme			×;				-							×	*	*
	dinamo pilcino de substantados			\$ +												*	<
	משונים ביינים ו			×					-					•		×	-
XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	CENTRAL CONTROL OF TAXABLE CONTROL			×				-			-}					×	×
XXXXXXXXX	Assess Catalog Catalog Catalog			×	, , , , , , , , , , , , , , , , , , , ,		-		·			-			×	×	×
	daments day to the Country of the Co			×					-	-	-				×	×	*
	demandadora to Picto Crease			*		-					-		,				
	denenta das lo Ceutricificado Dassar	,		4							- ;					÷	
Ш	annuals devides due to general medical condition	è	1	- -					-			,,,,,,,,,,,			×	×	
Ш	Charles bearing passage and control of the control	×		×			-	-							: :×	×	
X X X	confine deaths	×		×				-						,			
								-			3	×			:-	×	-

\$

EPO Munchen

			THE PROPERTY OF	Server States (Server)	New York of the last	E HE WOOD AND THE	POWERANTE	-	MODELLA RECEIVED	1	A CONTRACTOR	Albitraria (1840 VIII albitraria)	-	HOVOI CONTRACTOR TO SECURITION OF THE PERSON	1200000	
	- MONO	COMBON												-		l
	上級的	ISB 12 AUG-Antonomial of NS company	brancamos (MD)													
									•							
	5-HT2A.D4		Nuscainic receptor	emyloki nggragatlan Ethibilar	rotect dopeminary d cholmarys neuro	nceeting institutionisto recepto sensibility egorists	coério recepto agarésta	cABA' aganbi	EFBK* ncfrafon	Juppepu LEL	Coldum Charmit Modulato	, Adopauri	Soparche sporbs	MACHE: DAY	DA-upisko IAG- hebbler	IAG-D-re-upter Inhibition
Neilicat Ismeation														H	H	
							1	†		1			Ť	$\dagger$	+	
<b>ОСВОЯВЕН МУНАК ЧИВЕРШУКО: ЕМОПВИ: БУВИЕО ШАПОМ</b>	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
PARTICOCKITIVE MENTAU PIRORDERA (VELYRABIO) PARTO	_							-						-	-	
Tellettellettellettellettellettellettellettellettellettellettellettellettellettellettellettellettellettellette								-					×		1	
	×												×	×		
paychole dunders								-				- 1	-			
suppose furnicularity								-		-			×	367		
sum klam decries (autoling Pain Dander)	×					-	7	•		+			¥.	2		:
(actions doeder	×												×	×	-	
disactaive disactaire	×												<b>.</b> ×	×	i.	
scattlend gender idently desorders	×							-		-						
The state of the s	1					-	-			-				-		
and the state of t						•	J.			+			×	×		
capacity accordance average	-							-			*******		×	×	.:	
stanfordefal diordes	×									•			-			:
dauptive behaviour danders	×						-	-				-	<u>:</u>		+	
substance-related duorders	×												×	×	-	
esphony theorets	*												×	×	. ;	
entrantan paratri franchis a primari and a primari and a primari a	  -							•						-;	_;	
undsacial behaviour	×															::::
Dures werneral	×							-		-			+		<u>:</u>	
occupatoral problem	×														-	
Contract (1) to a sector	×						-	-								
academio problem	×		-												.;	
problem retited to obuse or neglect	×												×	×	-	
All Hill Control of the Control of t		_		4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4												
Marinalistication of the Stiff to an analysis of the Stiff of the Stif		_						-					×	×		
птанинайтийнициничениканкосфууствоговия																
- delitim		ĺ								-						:
Athernor Oberts			×	×	×	×	×	*	×	×	×				<u>.</u>	
statemental particle denotified			×	×	×	><	~	×	×	×	×					
encode Milital with although				2		×	X	× .	×	×	×					
darreds due to bead hauma			÷	3		4	÷			*	0				-	
durantia due to Partinson Disease			×	×	×	×	 	«×	×	۲×	×					
dengalis die to Nafagian Disesse			×	×	×	×	×	×	×	×	×				٤.	
OFFICE AND STATE OF THE PROPERTY OF THE PROPER			×	×	×	×	×	×	×	×	×			-	-	
entities dispersions are to an expension of the	*		}	×			÷	*	×	-	×	-	-		٤.	
unitable induced perdeting amounts disprise	×		×			4	0	-	0	4	÷	1	•			
mild cognitive impairment divertan	×		×	30	×	×	×	×	×	×	×		-			:
other cognitive disorders	×		×	×	×	×	×	×	×	<b>-</b>	×		-		Ļ.	
																:
									**********							

b	D
þ	Ö
١	_

The second secon		L																
	- OHON:	COPROL																
														Γ	KH12A	Literarid .	17 THE	degradate
		SHI2AD4:-Astrocals	CNS compound								- 1		ŀ	]	DEATE	Di-Artagoria .	Ottobald	
	Suma ion		Upto-074 Comptu	ningamanahan Iganda	rewenodádor Ne	ideali Line Derkibles of the R Veznos cobie Fect anns Minne I	-2.5	deredne AZe opter entster	TOXY.	de Gene	(verio estde) NSAO*	of beta Catholian in the bath	e de	CLERCOLLE	2 2	E S		
										†		†	t	1	+		1	
VERICAL INDICATION			+			1	1	+		Ţ			H	$\parallel$	H			
HOLGORDER WITH AN UNGERUNAIO EMOTION DYSKE EUULANGEN	×		×	×	×			<del> </del>	×	×	ř	+	×	×	4		4	
INSTANCES OF THE MENTAL UNITED SETS (CERTIFICATION SERVICE)	-	<b>-</b>	-	-	-	-	-	- }		-		<u> </u>	-	-				
י אינויינייניינייניינייניינייניינייניינייני			,			,				4	***************************************	ŧ	+	ļ.	<b>%</b>			
	×																	
astro Grades	×												+	<u> </u>			<b>%</b>	
presenting syndrone	×					+	+							Ļ				
son thirm Graders (ambiers Pela Dicader)	, ,	Ì			-	-								Ц *:	<b>3</b>			
Casacidin disciplina	×									i		j	Ť	÷	<b>%</b>		4	
served and condens the talky decorders	×		-	-										×				
dep Goder	† *		*******											<u> </u>				
Achitment disorders	†  -													-  -	7		4	72
. To any and the standard and standard							-			-	1	;	†	 	<b>%</b>	 犯	<b>%</b>	
etherbode/fall-decripts	×		4			4	4	-		+		+	÷	<u> </u>				
Garphie behalou deaders	×									-				Ļ			Ø	
suppression of the suppression o	†		<u>.</u>												3		7	
Promote College and Annual Property and Annual College and Annual Coll	×							-				;	:	<u> </u>	<b>%</b>			
principal	×						4			:		-	<u> </u>	-	<b>%</b>			
restrated laboration	×				1								•	  -				
Datament	† *		,			•		-						¥				
margari ema primare margari ema primare	†  -													<u> </u>			2	72
Charles of the stebler	×						-			•		;	:		<b>经</b>			2
matter a state of the state of	×							-		Ť		<del>;</del> .	:	-	<u>包</u>			
problems refuted by those or neglect	1	_	4			4												1 5
ququshilingan kalembili bili bili bili bili bili bili bili		_							×	×	*	×	×	×	2			<b>7</b>
MINISTRACTION OF THE PRINTER COOK THE CORDERS		•	1											;		1		1 2
atypo												:	:	+	1			
Althorn Chann							¥							×				
nchitacechalose per siste des esta			-			-	-			-				<u> </u>				
Market and Street													:	-! -:	7		4	
demants the to hard touch						-	-	-				•	:	+	<b>%</b>		<b>%</b>	7
dements due to Puthren Disaste							.,	***				;	Ì	-	<b>%</b>		<b>%</b>	
dements due to Heathgran Disease													1	<u>+</u>				
dements daes Pith Clinese			÷	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		-				-				<u> </u>				
collection by the contract of the collection of	×													×;	4		% T	
substance-baland pervising americ dicader	×												-	+	1		2	
mild cognifire impairment decrine	×						Ž	-						×				
בונות במבונים פונים ב	Y	-				4		4							[			
Hillingstringstringstringstringstrip PARKIN SON DISPARE		_	×	×	×	×	×							- -	4			

6-HT v serotonin 6-HT v serotonin ( recentor
SHTIA = serolonin 1A receptor SHTIR = serolonin 18 recentor
5-HT2AD4 = second 2A en dopamina D4 receptor
S-HT2C = serokanin 2C receptor
5HT3 a Berolonin 3 receptor
AMPA = sipha-emino-3-hydroxy-6-methy/ 4-tsoxezote proplenste
CINODs = COXInhibiling nitric oxide donators
COX a cyclooxigenaso
CUX-2 = cydocxigenase 2 CRF-1 = Confocyopin-Releasing Factor Receptor 1
Di a Dopamine 1
OZ a Doparning 2
DA = Dopamina
ERK a extracelular signal-glated kinaso GABA a gemma-minobittede odd
GABA-A a gamma-aminobutvic acid A recentor
GABA-B = gamma-aminobutyric acid B receptor
GPCR & G-Protein-Coupled Receptor
H3 a histomina H3-eceptor
MAC-A a mono-amino oxydasa A
MC4 a melanacorin 4 receptor
MCH = Melanin concentraling hormone
Mgluk e malaboloole glutamalo raceptor
M. E. meistonin receptor NARI = selective non-artrenation re-unitake Inhibitor
NaSSA e noradranergic/specific serotanergic antidepressent
NDRI is selective non-adrenatine and depamine re-uptake Inhibitor
NGF a nerve growth factor
NK1 o neurokinin 1 receptor
NK2 o neurokinin 2 receptor NK3 o neurokinin 3 recentor
NMDA - N-Mathw. D-aspartate
NSAIO = Non-steroidal anti-inflammatory drugs
PDE4 a phosphodies(ergse-4
SCT-11 = G protein-coupled receptor
SDA = Seroterin/Departing Antagents! SDR1 a selective constants and demonstration testition
SNDRI o gelocitivo servorin no sopranime no pero intentina CNDI soprativo servorin no servorina end dopanim e upitake intre
SSRI a selectiva saralanin rappiaka Inhibitar
VIB = vasopressin 1B receptor

Table 6		<del></del>	
COMPANY   Server   COMPANY   Server   COMPANY   Compan	History Pharmocrafices Percela Percela Percela Rain Scences Aftin Afti	Gravishthkine Gravishthkine Gravishthkine Gravishthkine Gravishthkine Beyer Be	The state of the s
BOSE BUNG BOOK BUNG BOOK BUNG BOOK BUNG BOOK BUNG BUNG BUNG BUNG BUNG BUNG BUNG BUNG	TARAMATARINA MATARIAN INTERNALIAN INTERNAL	ALANGER SENTENCE SENT	
COMPOUND  Floridation of the property of the p	See Propriet The Control of the Cont	SE-271046   Classification   Classific	WA 5000 A STATE OF THE STATE OF
ATIONS	Oggression Andely Parkinson Billsissis Author Autho	Abbelmes Districts Abbelmes District Abbelmes Di	
PHARMACOLOGICAL PROFILE  1 Stift republa enhance 2 SATI a gratul 3 SITI A gratul 5 SITI A gratul	SHITA spent BHTA spent BHTA spent BHTA spent G-SHITA straperist SHITIS straperist SHITIS straperist SHITIS spent SHITIS spent SHITIS spent SHITIS spent SHITIS spent	6 6-HTS actoports  6 6-HTS actoports  5-HTS actoports  5-HTS actoports  5-HTS actoports  6-HTS actoports  6-	I Independe A Sanceopte skingofd I Administration clease Shaha is developed skingofd I Administration clease Shaha is developed skingofd I Administration clease Shaha is defendered to the state of the
п. РН. РИОF.	14. 10 m.	8 101	
PHARMAC, GROUP (see everview hereunder) Abrocamberge Transitier Systems Abrocamberge Transitier Systems Abrocamberge Transitier Systems	Noncombiente Transmine Systems Noncombiente Transmine Systems Noncombiente Transmile Systems Noncombiente Transmile Systems Noncombiente Transmile Systems	Manoambragie Transmiter Systems Manoambragie Transmiter Systems Exclutory Amino Acid System	Adensativo Transmitter Spiem Amerinterio Transmitter Spiems Amerinterio Transmitter Spiems Memerinterio Transmitter Spiems Espieter Antro Act Spiem

Emphishment	PHARMAC. GROUP (see overview hereunder)	AL. PH. PROF.   PHARMACOLOGICAL DEDCE	Contract of the last of the la			
Control of group of the control of	Exclisiony Amino Acid System	(Semple)	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Mandre Decree   Mandre Decre	Degarie Mechanisms of Dementia of the Athetras Tune	el alleman de la companya de la comp	AOHO	methytakendale transdemal system		Marine Character of the
	and I william to the state of t	If emyod aggregator-hitelior	Abhener's Disease	Abanca Managaran India	description of the second second	Novem Proximize ducizas
The control of the	Frederich Calina	ici)thin mutation and ma	Athemer's Clorase	APAN	Herinal Tallian A haracters of	Newcoman
1   19   19   19   19   19   19   19	Manage and Annual Property of the Party of t	18 andregen receptor modulator	Female Search Desharding	Charae		Praces Pharmaceutical
	STEERING STREET, STREE	19 beta 3 advancecator agentsi	Demession / Audeto		Tressila - comments sedentiments	Ugand Pharmaceuticals
Cleaner Methods   Performent Cooperation   Performent Coopera	Chair Claram	20 Caldun Chanel Nobelster	Abhemer's Desses			SanofhSyntholabo
21		Caldun Cransi Modulity	Dodiners's Disease	inion iuo		Memory Pharmpooutloats
20   Control of the	Nondambrergo Transmitter Systems		CHAIRMIN COORD	Jairande		Novice Photographicals
Activities   Act	ErzymulicSystem		Sortzootreria			Small Control des
Activities   Act	Exclizion Amino Acti Setam	PATRICIA MATERIAL PATRICIA PAT	Patr	40785	and the state of t	Company of the Company
COCK 2 Hilbra   Path	Errenside Cast	ASIGNATION OF THE CONTROL OF THE CON	Athemer's Disease	NICESTUM PURE THE PRINTER FOR FOR THE PRINTER	Annual Landellist, Call and Landellin	statosti grano
COCA STRANGE   Part	Legillate Sprid	ZAICOX-2 Infulia	Pate		TO SOURCE GRADICALIST THE STREET	Misusian Pharma
COL2 bridger   Pan		COX-2 billing	9-1-1	negenno.		Pfter
COLOR DATE		COX2 InfoBre		ro ecouto		Piner
CONTAINED   Pan		- CHARLE AND	100	Valdecoulb		Office
COCK-PHINES   Prince   Princ		Division of the second	P. C.		THE PROPERTY OF THE PROPERTY OF	100
COCK PAINTER   COCK PAINTER   Pain   Variety   Pain   Pain   Pain   Pain   Variety   Pain   P		CUA-2 en oto	Pefin			MOTOR
20 COX 2 tability   Pain		COA2 Printer	Pots			Novards Pharmaceuticals
20 CON-Antibing for facetor (CHOLD)   Pain   AZGRIPH   Fill   Fill   Pain   AZGRIPH   Fill   Fill   Pain   AZGRIPH   Fill   Fill   Pain   AZGRIPH   Fill		COX-2 hithin	Pain			Pitar
COCK-MANING (The Cock of Grandson (CHC)	craymatics/ston	26 COX-hhbiting nitic oxide denters (CINDIN)	Dain			Abbatt
20 For I integrated		COX-tabilities not contra densities (CINPIPE)	1,00		376M do 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	AutoZenes
CFF   stabulant   Operation	Endocline System	26 ORF1 amounded	res	AZD417	The Public Commission of the C	4 stra Zenoen
Cost   stackers    Cost   stac		MDC ( a feed by	Depression		TITE SAME PARTY	Communication of the Communica
CPG   standard   CPG   CPG   Standard   CPG		Simple	Depression / Andaty			COVERTS POSTER SCALISCON
CPF straports    Depression   17200   Depression   17200   Depression   Depressio		Kimberie Laws	Organization / Aradely			ATTECH & JUNISON PROFILED
CEFF integrands		CV-1 antigority	Depression	rational designation of the second se		/lacy
Cort of statement   Cort		CPC-1 Bridgeshix	Demession / Andely	NELTAN		StanSmithfine
Control benefits		CRF1 anteganist	Decreeting Angles	CO 464 Cm		Veutorine Basdences
27   Di (Cespita ganta)		CAF I and a contst		Chipaesia Chipaesia		疆
20   10   10   10   10   10   10   10	Mondaminage Transmite Systems	27 Di nezadar annalei	.]			Phine
Discourted statement	Monominopic Transmitte Systems	29(D2 seconds mileacula				
10 statement   10 s		TO receipt and		philappide	Widtham The Control of the Control	and vaca outres
100 separati	Managraharda Transmittir Systems	Supplied to the supplied to th				A potent
10 arayonal   Cocho Depondres   FD 5641     10 arayonal   Performance		is unbana emisy		SS-201640	armena elektrikara	dray
Use staymant   Performer   Disastration   Performer   Disastration   Disastrati				16789 C		
100 and 00051   Parkinson's Drassa   Pro 60491		U.S. Bragana		85F.201640		
10 strate to the control of the co		Les target aris		3) 60491		
Distriction   Control		D3 antaganist		Sec. Soletie	7	
Margine initial   Cocate Departures   Cocate	Managements Towns with a S1	D3 artagarist		O Enge	7	
Shutton british   Perfection of Disease   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209   1437 17209	STATE OF THE STATE	30 DA matata tribitar		10000	2	
Stopentine sports    Parkinson's Disease   Advanced	Manager 1	DAudrico Intitiza		100 I 600	Z	ational institute on Dam Alexa
Perform Description Continued Contin	marginatic lightning systems	31 dopartina agords (		State of the second sec	Z	Own Plannamentales
Profession States Registration (Composition Configuration) (Configuration) (Co		dopartire aports	Designation of the second		0. 10 to 10	NA.
Contract of States resident and individual MAN (Amipo) by Act He form field to the fill the f		dodarma sonisi	B. A. S.	Committee of the Commit	60000000000000000000000000000000000000	then Dhome
Catheroding		documing ample)	1	colifice (Carlotter eters (carlotter)). The	756 256 464 1015 1915	Land Contraction
Victorian's Userso   Sarlanga   Parkinan's Userso   Salva Salv		decamine seconds		abenome	o prominently discounting an	THE STREET
PARTINATO DECESSO   PERMISSION     PARTINATO DECESSO   DALGAS,     PARTINATO DECESSO   DALGAS,     DEPRESSION   PARTINATO DECESSO     PARTINATO DECESSO   SANSO     SANSON   SANSON     PARTINATO DECESSO   PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO     PARTINATO DECESSO		Paragraph and a factor of the		atinian	3 0	100 PL
Parkstown Boszoo   DABJ873   Parkstown Boszoo   DABJ873   Parkstown Dazestown American Boszoo   DABJ874   Dazestown Parkstown Boszoo   DABJ874		destruction assessed		rampeode		AL PASTILLIAN DESIGNATION OF THE PASTILLIAN OF T
Pathham's Useza, Canardo Sa.V.333  Opression I Analdo Patham's Essays Patham's Essays Patham's Essays Patham's Essays Patham's Essays Patham's Essays Information's Essays Information's Essays Information's Essays Information's Essays		State of the state		MASS		ze
Depression / Analely SINSON Parkinan's Desais SINSON Parkinan's Desais SINSON Parkinan's Desais Investigation of the Communication Parkinan's Desais Investigation of the Communication of the Communi		CODEMING AGENTS		17.309	*	ę.
Perkitanti Disesse 533504 Perkitanti Disesse bronoufilia Perkitanti Disesse bronoufilia		apparating agonts!		32504	SS	thay.
Parkstonis Disease boundarylle		thropoentra and a second		19504	8	wa
Parkitzan's Deazes Jameses		(dopanino agoris)		1000	Sc	TANKE.
		dopanhraagonist		alian and an	No.	ovarils Pharmacounterin

\_\_\_\_\_\_

The content place   Content	BUADIAN GROUP (see averylaw hereunder)	III. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	- COMPOUND CONTRACT TO THE PROPERTY OF THE PARTY OF THE P	THE PROPERTY OF THE PROPERTY O	Centaur Phaimscaufeals
Signature   Sign	שליים מוספר (סים סיבורים)	IB	< activation				nicht Setystu, JPN Nettermunn, Bletz
Signitury Accounts   Signitury   Signitu	Enzymatic ayalam		Agrandi	(a Clistain		220mg 345	undberk
10 (10.00-)	Inhibitory Anthro Add System		RACA scorisi				epriecol
1000-Microsists   1000-Micro	Inhaltary Anino Add System	1000	Da. A mouthfulte				ansp-8wr/hetabo
Outstanding   District   Distri	Inhibitory Antho Acid System						VIV / Neurocrine
Old-Mark models   Dischard   Dischard models   Dischard		3	IN-Windship				desert
Old-Amendebus   Collection		Ó	HA-A modulater				dan Dhuamacairtenta
Old-Mark on that   Old-Mark on that   Old-Mark of the   August   Augus   August   August   Augus   August   August   August   August   A		0	BA-A modulator				ING PRESIDENCE SECURE
Old-March dalay			BA-Amedulitar		and the second s		Sepracor
CORPORATION   CONTRACTOR   CO			The Property of the Party of th		35P1/433V		Sanof-Swithstabo
Glab-Armonists   Fromth   From   House   Glab-Armonists   Glab-Ar		70	DA-A INCOME	Amelia marganta contractions	(5), 65, 1458		1
Class-A the obtains   Financial   Financ		8	BA-A modulator	Parcell I in a	(CP.3 TO TO TO TO SE 2)		tan oilei
1000-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-		15	BA-A modulator	Insormile			Yeurogen
Stickers   Department   Depar			DA.A modelete	Insumila	IN THE REAL PROPERTY OF THE PR	结	200
10   Control   Department   D		3	The state of the s	Angleh		: -	Lyanda
10 Gate-call the District Number of Control Department of Contro			(BA-A modulities			-	111111
10   10   10   10   10   10   10   10			ARA-B antagordal	Oepiteratur Animary		= :	Lagar
10	whitetory Anthro Add System		La sant tra Darkert Manneton Mc Factor	Perdinson's Diseaso	Hall Hills in the manufacture of the contraction of		National Institute on Orug Abuse
33   Other Designation   Article   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978   1978	Neurotropha System		The second secon	Pareta Denendente	molytapane		74,100
10   Reinborte   10	Cudenden Cultum	F -	OUTCOOLING STREET BY BUILDING		1 V354740		
Committee   Comm	Chuptus o'sauti	210)	schanata receptor entagonist	Anxiery	,0010		Rathe
Commence    Exchatory Antho Act Bystem		000 444120	Depression / Analely	THE THE THE WAY THE THE THE THE POT IN	TILL Second SA	Carreni	
Clip	Other/Unimown	2	CAMPAGE	demaster franchattel			Otestado
GR einig gridt	Cadados Civilors	410	R entagensi	1,111	0.00 345 70 4850 Sent Fall Life Control of C		
Address	Chullen of state	9	Rentzesolst	Department			Арроп
Application			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Atthebner's Disease	VR1:Z38		Abbott
15 August   15 A	strates and Tonand Its Britania	42,4	2 Anathra	Int. Late Change	ABT-634	The first of the f	
Common Bushiness		_	Antoporist	AZDENINI 9 MORES			Gefex Labatelone
Variations   Var			acerd no Dubatunes	Prementitual Syndrome	The Assessment of the Party of		Process & Camble Pharmaceuted's
Homerate and behavioral statements   Homeratural Statement   Homeratural Statement	Endocine System		Children over the second	Family Baxual Dyshuncten	The contract of the contract o	THE PROPERTY OF THE PROPERTY OF THE PARTY OF	Ger I shatabalas
Homewall Substances   Former's Statistical Continues of Process			bimgnel Bibsizince	Charles Displace	Line and continue out ogen A. Line and Continue	THE SEAT WILLIAM TO THE PROPERTY OF THE PROPER	1000
Formula Supplement   Formula			ormoned Bubstance	Frementantal Spinishing	The state of the s		Rosanto Pharmadelucias
Principle   Prin			Luciana Birbetanes	Fernal o Serval Dystunction	(Galostorona Her		Catany Pharmaceultain
			Dinibility of the size	Counts Se med Ovehreifon	tustostarone ge		The second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a section in the second section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the section in
			omonal Substance	The state of the s	melbulestoniende		NOVELLE PROGRAMMENT CONTRACTOR
			formantal Substance	Ferror & Se Aute Ly statute of	and the state of t		Sormy
Common and Communication of S.M.   Comparison (Authorities)   Funded style   Comparison (Authorities)   Co			determined Rightlanden	Ferral & Sazuri Dyshinction	CTGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG		WWS
Addition		WILLIAM LUCATION	Female Servel Dychucken	testastone gansdermal spilky		-	
A liborate to the consentiation of SAT   Department of Arithment   Part of SAT			tomonel dustance	Description ( Amount)	KW G059		
	of a confidents Tenestal Sections		nor sales broke contemplations of p-MI	4	PMD 145		
Digitality   August   Augus   Aug	Marounitalist and an		nergine briefs concentrations of 6-MT	Unprinsion (Albair)	91400		7
Accessive before contribution of 34ff   Operator   Accessive   Operator   O			Accesses hade concentrations of 5-MT	(Dapression / Anidery	27.100		,
1			Table to second ball of the	Depression / Andely	Tripiositie		Glass Smith Kinn
A ST   Control of Street   Control of Street			NG 6219 Cran Concasting and Call	Altheimen's Discone	rosigitazane mala ale	T. ELF SCHREITERIN Couster	Conhelm
A   Parks	Endandes System	45	nere salighted in sentimery	Dadana's Manes		michigan de entitient discount	- Control of
			Abkor of the mixed Greage Alberte family	Printed to Contract			Avensa
	Englymand bystom	67	rderfauth-1 bets converting enzyme tritibilor	Pch			TRVA Pharmaceuticals UttA
Solution   Complete   Control	Enzyerado Systam		and and	Perthron's Disease	יים מושים של היים וויונים וויים וויי	The state of the s	Valentia
Solution   Compaction   Compa	Monoambougle It ansmitter Sycients		CALCOUR Complex	Pertinson's Discose	GRZ13487B		National Institute on Drug Abuse
A   MAC   A   MAC   A   A   A   A   A   A   A   A   A	Other / Unknown	2	וממיםות בחומים	Cocaine Dependents	Ng 2350		Datem Carneth
MADOR A LANGO A LANG	atonographs Transmitter Systems	O CO	LAO relytake full bilde	070	NB 2559	" THE STANDARD STANDA	Modern Comments
1 MAD A MAD OF COURTS   1 MA	Annual Property of the Parket Property of the		LACO reuptate Intificial	NAME OF THE PERSON OF THE PERS		thing out of the little of the little	PART PARTIES CHIEF IN PARTIES IN
14,000   Pubble   Department    Monstath ergo It amonder of white	150	NAO-A & MAO-D reuptake Inhibitor	CHOND	P. D. D. De and come a collection		Some cal	
MAC   Packing    Memorand regio Transmener Systems	83	UACA BANNOT	Depression	California de la companya del companya de la companya de la companya del companya de la companya	The state of the s	Amerin Pharmoonticets	
All Continues	Nonsanta ergic Transnetter Systems	20	A. C.	(Poddness's Oferson			TEVA Ohrmacendeets USA / Land
Aloca interpretation   Parket 1991 Discuss   Anthonica			MACH INDICAT	Darthraph Phases	THE REAL PROPERTY OF THE PROPE	TOTAL BELLEVIEW STREET	The Charles of the Charles
Si   JANG B   Leughan lehibilion   September   Septe			UAO-Binhaiter		- aleandila		Maridu Filminguaphenia
1962 of other other   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964   1964		13	MAD-B re-uplake inhibition	Parensons Meass	1,000		Taltho
100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100   100	Mendaminately Transmiller Systems		the anti-confete	Depression / Andrity	MCLUIX		Bynapia
15   15   15   15   15   15   15   15	Peolderde Transmitter System	Ď	West attractions	Dervession	SNA-786	A MARINE CONTRACTOR OF THE PROPERTY OF THE PARTY OF THE P	
Softmatiscent to receive a spent   Department of the state   Department of the state	Paniderela Transmitter Sissem	2	Machine antagonal	biomets.			annua .
Contraction		25	malstonin receptor agontsi	discussion of the same of the		25 to 30 to 4 to 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	- BAIMB!
67 May 6 agests Annello 1	Endocus ayarıs		metatradin racester adontist	Depression / Andely			Prescient
Althorace   Althorace   Althorace   Althorace   Column	1	11-to seeds	Anglety	PARTER AND THE PROPERTY OF THE PARTER AND THE PARTE		Asmoth Smithstabo	
Contract in a state of NUP   Althority (CE)   States (UE)	Endatory Amino Add System	B	The state of the s	Althornora Cineass	Market Strategic Land Committee Strategic		Canada Calvaha
51	Nermitroship System	99	CHECK TO SUITE OF THE PARTY OF	At-to-Lines ( CO) / Cleares (UR)		PRINCIPAL SHIPS HELD STATE OF THE STATE OF T	and the state of the
Colorest	Total Sale State	5	Muscadala receptor puodel apportit	Augustina de la simbilita de l	te hounds		P(Tz0)
Auto	EXILIDITY ATTEND AND DISSERT	an	542	Depression / Anxiety			ED UIV
Coprosiden   Chipagilish (1971-1971 And 1971-1974 And Attachment	Monaturin ergia Trensminar Systems		C) C	OHOV			ii paret
ADVD   165U88   155U88   155			MAIN THE PROPERTY OF THE PROPE	Percenter	STATE OF THE PROPERTY OF THE P	i e io il kied Prefittie di limite	
AUND			NAR	The state of the s	88.50		COTOSMUNAN
Copression / Analety (Opto 1020)			NAR	AUND	2000		Abbeil
Operatelon / Andaly			ZAS.	Depression / Anniety	0070/14/00		Abbot
				Operetajon / Andsty	A75200		

18.5534	PHARMAC, GROUP (see overview hereunder)	nr. PH. PROF. PHARMACOLOGICAL PROFILE	WAIN WORKSTOWN			
Strainmentation	Mondaminerge Transmiter Systems	NSSA.	STOLING INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
State   Commonwealth   Commonwealt	Monaminente Transmiler Systems	62 MDRI	Insomit		Show The Property of the Parish of the Paris	L
Electronistic	Hourelmmunophiln System	G and mineral in the sale	Urpress fan (Dipolar disor der)			Character C. T. Line
Statistical Content	Admostra Transmiller Sydam	מים ואים מיווווות משונים וולימים ו	Parkinson's Di seaso			Cataloninana
Statement   Stat	Partidante Treasmile Contra		Periodon's Disease			Guitord Photom acousticals
State   Comparison   Comparis	Married Lines and Control		Schbobroria	Company of the state of the sta	The state of the s	
68   Recting the part	LIGAL C TURO DO COLL		Michelman's Pitana		DOZONG GENYTHER THE	
10	Exteriory Amino Acid System	67 recount abety taken necessor answers	DECEMBER OF THE PARTY OF THE PA	(name growth factor (NGF) gate thought	A	
10	Exclisiony Amino Acid System	GR Modification Description	MURIT	SER 1750 (SERVICE DE LA COMPANION DE LA COMPAN		
70   Policy and   1995   Policy   Pol	Pedidente Tramminy Sydym	on lateral algebra	Athelmer's Cisease			depretoo/
1000 services   1000 service	Dealer Literature Committee	da inn antagonia	Derretts land And Alv			Abbeit
1   NOTION SECRETARY     NOTION SECRETARY   NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY     NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRETARY   NOTION SECRE	recognic Iransman System	70 MK3 antraonts	1000		OF THE STATE OF TH	Sanna-Swotherston
1   NOTA SEPARATE   1		NK4 antimutes	SHIMMON	Osanetani	internation areas areas areas	200
MOLA Management   Machine   Microscope   M	Extistary Amino Add Switten	10101	Schingfiveria / IBS / Own active bladder		TELEVISION FOR THE PROPERTY OF	
NULL AMERICANI   NULL	The Constitution of the Co	71 NAUA entaganisi	Antlety			Ghos mithline
NUMBER   N		NUDA antagord st	Alabaha da Prana	10CF1/4038		Septecal
Total account   Total accoun		NUIDA entlannie!	August 3 Change			1,11,11
12   NALON metapores   19-20		Nation Application of the second of the seco	Oppositon			CONTRACT A POINT LEDON DIOVES
12   MSAD   12   MSAD   13   MSAD   14   MSAD   15		100000000000000000000000000000000000000	Per			Windbook / Forest Leboy attacles
18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   18.540   1	Charles of the Control		Daggarate			Lundbeck /Fortest Labor stories
18.5.00   18.5.00   18.5.00   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5.10   19.5	Cutyment o Januar		Dolo	Contentit		Ed.
13   15   15   15   15   15   15   15		NSAD	7.0	meopean		Boshing Londham Dhamasan Land
73 and a majorst		GYSN	15	piovicam	ı	מנושיות ביו למיוחון ביות וופרטותכם
73		W SIT	Athemer's Disease		Particular Dolland Colorana	Tuered in
1	Eschifor Ambo Avid Rooms	ALCOHOL: A CONTRACT OF THE PARTY OF THE PART	1	AN CREATE THE PROPERTY OF THE		Mynad Genetics
14 optid special	THE CARACTERIS	73 gradd antagarist	Acchailthen Danandenna			Medinos
14 optid species		opold antigorist	Owel Alexander			Orac Abras S. diverse
10   Policy of a post   Cocasto Departure	Extractory Amino Acid System	74 contannia	הייייאוריים הפטבוספונים	Jorgan natherane microcapules		Tive
1000 Squares   1000		and a second	Attiety		Paragraph of the state of the s	and a second
10   10   10   10   10   10   10   10			Cocahe Dependence			Inducts / Forest
TPE 4 Inches   TPE	Francis Cut-		Schizobrenia	C Kolm		Hatlonal Institute on Drug Abuse
PEE   FANDER   PEE	ביי שוויים פי שוויים	POEAMEND	Developer	Luck		Estavo
PDE 6 lend is   PDE 6 lend i			Other Co. Classes	(CIC)		Yeuro
Poptide			DECOMING MINISTER	MEM 1917 (R1497)		John Hamoni Dram
Percent   Perc	Protect Franchier System		Dental Con	MEN 1917 (MI487)		The state of the s
Periods   Peri			Deposition		The state of	Wend I crem ory white
The period of the second by the second part of the second by the secon			Auften			interpretation
77   Prospections A 2 biblior with capacies to biblior softly   Department of the softly   Departmen		and address	Female Sexual Dysfunction			epigen
Proprietion of Standard Production of School Prod	Ertythatic System	Dominal	Athemar's Disease	belo-sheet broader executes		Tiath Fechnologies
Proceedings A 2 baking with capsus lets his a solidy   Dayses in Novin Color		Poznesier			lerano	
Propodupos A 2 tebbios with courses by like retire)   Shaper of the course of the co		Prospholpaso A 2 hobbler with cascass (res him and why	Democrate Mandre diese des		CONTRACTOR SECTION	Archile
18   Product of Judica   1   19   Product of Lands			ALM COLOG OET	LAX-1016	III. Latin and American	e.mela
Protest and E   France County   Ref. 10 (65-64)   Ref. 10 (65-64	Actesidas	Produce of tribline		CARtofa		America
Found Stand Order Control   Found Order   Found Order Control   Found Order   Found Orde	Endocrine System	79 constrained a			STATE OF THE PARTY	Branco
Formack Stand Distances   Formack Stand Stan		Destroy of the				- Labracan
Bit   Procession   Architectures   Architect	Neurotrophe System	rama gamu		તે.	THE WAR STREET, STREET	MS
Procession	Extlatory Anim And Sydem	Services communicate and challenge neurons		TERMENTAL PROPERTY.	A THE PROPERTY OF THE PROPERTY	6xMed
Perfeature   Perfect   P						anoli-Synthetato
Professionation   Professionation   Professionation   Professionation   Professionation   Professionationationationationationationationat		Psychostinutant				chalon
Pychastmidant		Prychostandan				the Physics and and Boundanies
## Control   Co		Psychostlandant	Litheracutus	9		and an
Certasion   Amely   Incocabomile	Mandaminente Transmiter Systems	PINE	Cocatris Dependence	HOGENET.		in the state of th
Departed Nation   Industrian		Dille	Depression / Andely	noclabenido		SIONE INITARE OF DRUG Abuse
Certasher / Ardery bioXXX 使用低温性 ( ) 在				parather	٦	ocho
Depart in Caroston F. 16554  Depart in Caroston F. 16554  Depart in Marie Caroston F. 16554  Depart in Marie F. 16554  Depart in Marie F. 16554						anol-Syntheta to
Depart Mariety Granding Depart Mariety 18 8559  Depart Mariety 18 8559					3	mof-Synthetabo
Depart and Articles (charalers) Depart and Articles Rs 5159				POLATON F.16654	}_	A Paris
Leponsson / Aradery Rs 8359				imaratana	T	THE PERSON NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TWO IS NAMED IN COLUMN TW
				38 6359		

;+3292602345

PHARMAC, GROUP(see overvlew hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSERANGE	COMPANY
Charlibian	10	SCT-11 modulation	Degreeston	SNEC2		Synaptic
Phocondoonic Transmitter Switche	2	SDA	Schtzophrenia	quedaphe		AstraZeneca
		YOS	Schropwerta	laripiprazolo		Bristol-Myron Repubb
			Schnophrenia	risperitione		Johnson & Johnson Pharmaceulge
			Schloghrenia	zolepino		Knot / BASP
			Schrophrenia	olenzapho		my .
			- 1	dozapins		NOVIUS PARTIBLE CUICEIS
			- 1	dprastform		Line
		SDA	Depression (Bipolar Matritainence)	ofenzaphe	3	lea Lany
			- 1	December 1		diamination of the state of the
				AND REPORTED TO THE PROPERTY OF THE PROPERTY O	2	High Amena Programa
		SDA		glenzapino		EDUTY
		SOA		ariplorazolo		distribution bearing
		SOA	Schlzophenia	quedicpine jumatelo (grandes)		AstraYonen
		Vas		(oustopins fumatelo (sustante detase)	HINDERSON TO THE PROPERTY OF THE PERSON THE	Countries of Phones Disconnected
		YOS				Section of the sectio
		YOS			LE MAZINO NICHIMINITALI	Contracting and the state of th
		VCS		Rodendono	Tarestance constraints	Ti Oursean
		SDA				Control Controlled
		YCS	Schzopterda			Colons
		YOS				Marian
		SOA		DCGGCTGC CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC		Similano
		SDA	SCHOOLINGTIA	SIA-1-3480		Lundbeck
		SDA	Schoolmena	10.01.131		6
		SDA	Schoolmerde	BSF-18039		Simber
		SDA	Schooling	מיומילי		Sanda Kathelaha
Astroprulnegic Transmitter Systems	83	E	Depression / Antiony		THE PERSON NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TRANSPORT NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TRANSPORT NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TRANSPORT NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TRANSPORT NAMED IN COLUMN TWO IS NAMED IN COLUMN TWO IS NAMED IN THE PERSON NAMED IN COLUMN TWO IS NAMED IN THE PERSON NAMED IN COLUMN TWO IS NAMED IN THE PERSON NAMED IN THE PERSON NAMED IN TH	Ilishedno
Nanoaninegic Transmitter Systems	98		Depression		PARTERING TO PROPERTY OF THE P	Sandification
		Second messenger beta agonts	Depression	State		Smoth Synthetabo
		Second messenger beta egonisi	Delices and	Chivalismii		SandaSvilhebbo
		8	Unsomna		I DESCRIPTION	Little Control of the
Endocatio System	80	Secreth pancreate homone	Andry			C. Hannes
		Bestedi panssalis homene	Behrochane			Veb. Obulo
Exclusory Amino Acid System	9	I skama receptor agontst	DEPENDENT	NEW PARTY OF THE P	Tall Television	Preda
		Symb receptor ogonisi	Anslete			Prodix
	8	design of the special	Descripto / Angato		10 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	REND Humaceuteria
Exclusory Amiro Acid System	8	Squitte recentor antagoods.	Schoolynein			Hirti Ganoft-Syntheteto
A Contract of the Contract of	8	SCOVE I	Attremer's Disease			Bochingar Ingelicin Prinmacade
Mender and the residence of the second		893	Depression / Andely			
		SWOR	Abtremer's disease			מטא
		2025	Depression	DOV 21,947		) 200
		SKORI	Depression	MAN 6652	and the second state of the second second	McNel
Abramathamila Tenteralities Surfaces	6	SNFU	Oeprossion			u differe Fabra
		SNR	Oppression / Andely	Instandane		Medd Jornison
		SNRI	Depression / Andely	Gingtaphio	Calling with the	Weyds
		SNRI	Depression / Anglety		a,	Warn Comment
		SNR	Depression / Andaly			America (F)
		SKRI	AOHD			Till Till
		SNRI	Depression / Awiety		, imagosofiche culturatura	in. Dona
		SNRI	Depression			Lundberg
		SNR	Depression	(blognam)		LUMBOCAL PROPER
		SNRI	Depression	Isndamine		Taylou
		SNR	Depression	LY 115.62)		, Tara

PHARMAC. GROUP (see overview herounder)	III. PH. PROF.	ш	MAIN INDICATIONS	COMPGUND	DOSPRANCE	Coupany
Mondamin regio Transmiller Bystems	1	92 B9Ri				Open of the Party
		9SRJ	Depression ( Analoly		THE SOUTH STATE OF THE PARTY OF	Management County of the standard
		8874				THE PROPERTY OF THE PROPERTY OF THE PARTY OF
		SSRI		unaturanteur	HETTER HEALTH PERSON	W. Darlow
		SSRI		Bacamatha		Calpatient
		888		Section 1		Of paren
		At the state of th	hobbal		differential lighter and the second	Piller
		SSR				BONDY
		888		Comments deposited to the contract of the cont		HILLIAN CHECKER STATE STATE STATES
		RSS	Determined Ameloby	CHINACHIES THE PARTY OF THE PAR		Fortolen
		NS N	December	miraching.		Novertia Pharmacaudorda
		Habel Habel	Certamon	VPPOT3 (elsa latavan as CPC-14523)		Vdo, Ourka
		NICO PROPERTY	Ucpression / Arciery	EAID 60543		EMJ Phemacoudeals
		NO.	Depresalan / Antialy	cettdantho		Jackelind
		200	Depression	Lu 35-138		Similarit
		GGR	Depresulan / OCD / Pain	1,7214,231		The state of the s
		838	Depresalon	LU AA 21-dau		1
		9981	Depression / Amile's	Countries		Lundridge
		SSR	Depression / Arulah	Information in advance in comme		,
		SKKI	Demarston / Angleto	Carolina de Caraldos para de Carolina de C		Sempt-Clibptcoma
Peptitage Transita Bysten		C) Substance Processor (NXII) entangelist	December / Angles	THE STATE OF THE PROPERTY OF T	With the second	Yananouchi
		Substanc P receptor (NK1) antanonist	Denmarken / Braink	יאוסלינין מינות כזהיות יהות ותיונים ודיות ותיוחים לאינטיום לעל פינעויים ואינטים אינטים אינטי	11. 19 di Lo i i Viro biada libi nel	Mack
		Substance Precedent (NK1) aniacontat	Demonster & brains	Children		Takoda/Abboft
		Substance Processor (NK1) anisportal	Deutschin / Amilah	CHONOLO I		Ghaognikkina
		Substance Preceptor (ARCI) aniance (s)	Description of the state of the	(Action of the Control of the Contro		OlaxoSmbh/kina
		Satabac Precentar (NKT) entracedes	Description ( Academy	14-12/121		Phror
		Substance Properties (NIX1) entermies	Deptersion Augusty	K0/3		Koche
		Schalter Desember Miles order	Concessor Amany	SW6/9709		CtaxoSmthKine
		Paratime Discouring Paratiments	Democran Arach	GW623298		Gbrosnidacho
		Side tree Describe (MA) and pass		67,876.9		ClassSmithtine
Other Uthingum		and hearth.				GardSmitheding
Peptidentic Transmitter System		Claritate halls and security				Elm Phumocesseals
Other / Unferown		Standard Community	Leginssion / Articlety			Remit-Syntholyto
		Improve				Hetshil-Myons Boulto
		tradensen				
		University	ravinson bysamo			rivax
		Unknown		<u> Karenderikinkinkinazan</u>		Ogrnon
		urborown		Orto Mie/		Олдзіки
Endoctine System	1			and in the second		Pdzer
Infibility Anino Acid System	9			STREET NAME OF STREET		Sunos-Syntholabo
						Pittor
					ATHORISHOTATES DESCRIPTION	Pitter
Office / Unforcem	6	99 yomsropherin	tree.	arena		Pittor
						Phenn Phamacondeds
THE STATE OF THE COMPONENT WORKENS ON THE	밁					
Antho Add Transpitar British						
Menoning Transfer Co.						
Exchine Antho Antho Anthony						
İ						
l						
Admycha Trepanitor System						
Endocate Bratom						
Engine le Byelen						,
Narvo Cell Function System						
Nouratraphic System		8				
Neurophin Bystom	0110					
Patrogenia Mechanisms of Dramenta of the Atheimer Type						
I VIMIUM STACTES						

### Examples

5

25

## Example 1: Measuring pKi values of test compounds

In Table 1, the pKi values of test compounds are given for each of the dopamine receptors, 5HT receptors, adrenergic receptors and the histamine1 receptor. The affinity of test compounds for the respective receptors has been performed according to conventional procedures known in the art.

An indication "0" means that no affinity has been measured between the test compound and the receptor.

The columns displaying the pKi values for the D4 and the 5-HT2A receptor are filled with dark grey. pKi values between 8 and 9 and higher than 9 are represented by light grey boxes.

# Example 2: Foregoing pipamperon-citalopram treatment in major depressive disorder: a placebo and active controlled period finding clinical trial

Table 2 represents the set-up of a clinical trial comprising for treatment groups:

Group Pic – Active / Day 0 represents the group receiving 10 mg citalopram, twice a day, starting the first day (Day 0) of active treatment in the clinical trial. This administration regime is also indicated as the mono therapy.

20 Group Pip - Active / Day 0 represents the group receiving a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the first day (Day 0) of active treatment in the clinical trial. This administration regime is also indicated as the non-foregoing combo therapy.

Group Pip - Active / Day 4 represents the group receiving 4 mg pipamperon, twice a day, starting the first day (Day 0) of active treatment in the clinical trial, followed by a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the fifth (Day 4) day of active treatment in the clinical trial. This administration regime is also indicated as the foregoing therapy with combination therapy starting after 4 days of active treatment.

30 Group Pip - Active / Day 7 represents the group receiving 4 mg pipamperon, twice a day, starting the first day (Day 0) of active treatment in the clinical trial, followed by a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the eight (Day 7) day of active treatment in the clinical trial. This administration regime is also

indicated as the foregoing therapy with combination therapy starting after 7 days of active treatment.

All subjects also undergo a placebo (PLC) run-in therapy, administered during a period of about 7 days before the active treatment starts.

- During daily (D), weekly (W) or monthly (M) visits, several parameters are measured.

  Under NECT is to be understood: Neuronal E-clinical Trial = Vesalius Expert development for this trial which includes the bottom-up measurement of:
  - In- and exclusion-criteria
  - Functional status evaluation
- 10 Medical history
  - (Pre-)treatment signs & symptoms
  - DSM-IV rules for diagnosis & efficacy
  - HDRS-28 (Hamilton Depression Rating Scale 28 items)
  - Medical resource utilisation
- 15 Pre-trial & Concomittant medication
  - Drug administration
  - (Serious) Adverse events
  - Admission to the acute and extension phase of treatment
  - Right flow of the trial

20

30

35

# Example 3: combo pipamperon-citalopram: therapeutic use in Major Depression

### 25 Purpose

Pipamperon (1'-[3-(p-Fluorobenzoyl)propyl]-[1,4'-bipiperidine]-4'-carboxamide), the active ingredient of Dipiperon (Janssen-Cilag B.V), administered to patients in a dose ranging between 8 and 12 mg is claimed via its specific pharmacological properties to be a booster of the antidepressant effect of the selective serotonin re-uptake inhibitor citalopram. Preferably, pipamperon is administered daily at least 4-5 days before administering said antidepressant. The mechanism of boosting of pipamperon has to deal with (i) the selective affinity for the dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors, and (ii) the selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors. This semi-naturalistic open label study investigated the efficacy and tolerability of the combo pipamperon - citalopramin the treatment of patients with major depression.

### **Details**

Design:

Semi-naturalistic i.e. inclusion of every 'natural' patient in an outpatient

practice but without concomitant use of mood enhancing drugs, open

label

Control:

No

Phase:

Phase IIa - preliminary Proof of Concept

Location:

Belgium - Research Centre ANIMA, Alken

End Points:

Assessment scale scores, Hamilton Depression Rating Scale 17 items,

Reduction, Response, Remission

Medication:

Exclusion of mood stabilisers, antipsychotics (typical and atypical) and

other antidepressants

### Subjects

Туре	No.	Sex	Age
Patients	23	10 male & 13 female	23-80 (mean 47) years

Characteristics: patients had a major depressive disorder according to DSM-IV criteria, 5 with or without a chronic course and a treatment refractory state towards another SSRI then citalopram.

### **Treatments**

15

PIP-CIT<sup>1</sup> add-on: citalopram from day minus 60-20 - pipamperon from DAY 0 10

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon <sup>1</sup> Citalopram <sup>1</sup>	+ Pip.: 8-12 mg/day - Cit. 40 mg/day	: <sup>20-</sup> PO	bid	8 weeks

1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

PIP-CIT<sup>1</sup> fore-going 1-5: pipamperon from day 0 - cital from day 1-5

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon <sup>1</sup> Citalopram <sup>1</sup>	+ Pip.: 8-12 mg/day - 40 mg/day	Cit.: 20- PO	bid	8 weeks

1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to 20 clinical response.

197

PIP-CIT<sup>1</sup> fore-going 6-8: pipamperon from day 0 - citalopram from day 6-8

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon <sup>1</sup> Citalopram <sup>1</sup>	+ Pip.: 8-12 mg/day - 40 mg/day	Cit.: 20- PO	bid	8 weeks

 Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

### Results

	PIP-CIT add-on  After 20-60 DAYS (mean 33) (n = 5)	PIP-CIT foregoing  1-5 DAYS (mean 4) (n = 15)	6-8 DAYS (mean 7) (n = 3)
Mean Used Medication			
Pipamperone	9mg/day	10mg/day	11mg/day
Citalopram	30mg/day	26mg/day	30mg/day
Depression scale scores			5
HDRS 17-item total score			
baseline	29	23	28
endpoint (week 8)	4	5	11
diminishment at week 8	-25 (+8/-9)	-18 (+8/-8)	-17 (+17/-17)
% reduction at week 8	86 (+14/-12)	80 (+20/-30)	61 (+39/-61)
response <sup>1</sup> at week 8	5 (100%)	15 (100%)	2 (67%)
remission <sup>2</sup> at week 8	4 (80%)	10 (67%)	1 (33%)

- 10 1. Response = ≥50% reduction in HDRS 17-item score;
  - 2. Remission = HDRS 17-item score < 8

Notably, the results obtained are highly significant since the variability in every group is distributed evenly around the mean.

### Add-on PIP-CIT

15

Figure 1 schematically depicts the "add-on" treatment with pipamperon 8-12 (mean 9) mg (bid) after treatment with citalogram 10-20 (mean 30) mg (bid) during 20-60 (mean 33)

[] []

10

15

20

25

30

35

198

days (PIPCIT ADD-ON) with HDRS-17. Totalscore is 29 at baseline in MDD in comparison with the standard efficacy of antidepressants in clinical trials according to Khan et al. (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 2 schematically depicts the HDRS-17 change from baseline in the combo pipamperon as "add-on" to citalopram vs SNRI (duloxetine) in Major Depression. Treatment with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n=5). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Figure 3 schematically depicts the remission rates (HDRS-17 <=7) with the combo pipamperon as "add-on" to citalopram vs SNRI (venlafaxine) vs SSRIs vs placebo in Major Depression. Treatment with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n=5). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with placebo is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Psychiatry (2001) 178:234-241).

### Fore-going 1-5 PIP-CIT

Figure 4 schematically depicts the "fore-going" treatment during 1-5 (mean 4) days with pipamperon 8-12 (mean 10) mg (bid), followed with the combination treatment of pipamperon and citalogram 20-50 (mean 26) mg/day (bid) (PIPCIT FG 1-5) in MDD (HDRS-17 at BL = 23) in comparison with the standard efficacy of antidepressants in clinical trials according to Khan et al. (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 5 schematically depicts the HDRS-17 change from baseline in the combo pipamperon-citalopram treatment with a "fore-going" treatment of 4 days with pipamperon (10 mg/day) vs SNRI (duloxetine) in Major Depression. Treatment with the combo pipamperon-citalopram with pipamperon 8-12 (mean 10 mg/day) (bid) 1-5 (mean 4) days

before treatment with SSRI (n=15). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Figure 6 schematically depicts the remission rates (HDRS-17 <=7) with the combo pipamperon with a "fore-going" treatment of 4 days with pipamperon (10 mg/day) vs SNRI (venlafaxine) in Major Depression. Treatment with the combo pipamperon-citalopram was with pipamperon 8-12 (mean 10 mg/day) during 1-5 (mean 4) days before treatment with the SSRI (n=5). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with SSRIs is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with placebo is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241).

### Fore-going 6-8 PIP-CIT

Figure 7 schematically depicts the "fore-going" treatment during 6-8 (mean 7) days with pipamperon 8-12 (mean 11) mg/day (bid), followed with the combination treatment of pipamperon and citalopram 20-40 (mean 30) mg/day (bid) (PIPCIT FG 6-8) in MDD (HDRS-17 at BL = 28) in comparison with the standard efficacy of antidepressants in clinical trials according to Khan et al. (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

20

25

15

10

Figure 8 schematically depicts the HDRS-17 change from baseline in the combo pipamperon-citalopram treatment with a "fore-going" treatment of 7 days with pipamperon (11 mg/day) vs SNRI (duloxetine) in Major Depression. Treatment with the combo pipamperon-citalopram with pipamperon 8-12 (mean 11 mg/day) (bid) 6-8 (mean 7) days before treatment with SSRI (n=3). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

### Comparison "add-on" vs "fore-going"

Figure 9 schematically depicts a comparison between "fore-going" and "add-on" treatments with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in MDD in comparison with the standard efficacy of antidepressants in clinnical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

35

;+3292802345

21-10-04;22:44

5

10

15

20

25

30

Figure 10 schematically depicts a comparison between "fore-going" and "add-on" treatments. In particular, the HDRS-17 change from baseline between "fore-going" and "add-on" treatment with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SNRI duloxetine in Major Depression is depicted. Treatment with the combo pipamperon as "add-on" to citalopram, with pipamperon 8-12 mg/day (mean 9 mg/day) 20-60 (mean 33) days after treatment with the SSRI (n=5). Treatment with the combo pipamperon-citalopram, with pipamperon 8-12 mg/day (mean 11 mg/day; bid) 6-8 days (mean 7 days) before treatment with the SSRI (n = 15). Treatment with the combo pipamperon-citalopram, with pipamperon 8-12 mg/day (mean 10 mg/day; bid) 1-5 days (mean 4 days) before treatment with the SSRI (n = 15). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein et al., (Clin. Psychiatry, in press).

Figure 11 schematically depicts the remission rates (HDRS-17 <=7) in a comparison between "fore-going" and "add-on" treatment with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SNRI venlafaxine in Major Depression. Treatment with the combo pipamperon-citalopram was with pipamperon 8-12 (mean 10 mg/day) during 1-5 (mean 4) days before treatment with the SSRI (n = 15). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with pipamperon as "add-on" to citalopram, with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n = 5).

The intention-to-treat / last-observation-carried-forward analysis showed a high therapeutic efficacy according HDRS 17-item in all the treatment groups. This was especially true for the 'add-on' group probably caused by the longer treatment with an active antidepressant (+33 days). The huge therapeutic effect observed in the 'PIP-CIT 1-5' group present for at a mean dosage of pipamperon of 10 mg per day and administered the first four days of treatment without an active antidepressant, indicates the boosting effect of pipamperon on the SSRI citalopram at an extremely and thus unconventional low dose. Only 1 patient discontinued treatment due to a lost of followup.

### **Adverse Events**

Side effects (patients)	PIP-CIT add-on	PIP-CIT foregoing	]
	After 20-60 DAYS (mean 33) (n = 5)	1-5 DAYS (mean 4) (n = 15)	6-8 DAYS (mean 7) (n = 3)
Discontinued treatment due to adverse events	0	0	0
By system:			
body as a whole	o	0	0
central and peripheral nervous system	1(20%)	4(26.6%)	0
gastrointestinal	1(20%)	5(33%)	2(66.6%)
musculoskeletal	1(20%)	3(20%)	0
psychiatric	0	0	0
respiratory	0	1(6.6%)	0
skin and appendages	1(20%)	2(13.3%)	1(33.3%)
vascular	<b>., 0</b>	1(6.5%)	0
urinary	0	1(6.6%)	0

Laboratory parameters, ECG, bodyweight and vital signs were not measured since this was a naturalistic study.

### **Assessment**

### **Outcome**

Efficacy: the 4-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day is comparable to the add-on combo pipamperon-citalopram.

10 Efficacy: the 4-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day is larger than the 7-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day.

Efficacy: the combo pipamperon 8-12mg/d - citalopram 20-40mg/day is larger than the in the art known antidepressants SSRIs.

15

### **Tolerability**

**Tolerability:** the 4-day fore-going treatment is comparable to the 7-day fore-going combo is comparable to add-on combo pipamperon-citalopram.

Tolerability: no discontinued treatment due to adverse events.

# Study Messages

The boosting effect of pipamperon at an extremely unconventional low dose on a SSRI is indicated since the efficacy of the 'add-on' and '4-day fore-going' combo 'pipamperon 8 -12 mg/d - citalopram 20 - 40 mg/day' is in this study as twice higher as known in the art in the treatment of patients with major depression.

The combo pipamperon-citalopram is generally well tolerated in patients with depression i.e. at least no specific added adverse events were occurring by adding pipamperon at the doses used in the study.

15

10

Example 4: combo pipamperon-citalopram: therapeutic use in Obsessive-Compulsive Disorder (OCD).

### **Purpose**

5 (1'-[3-(p-Fluorobenzoyl)propyl]-[1,4'-bipiperidine]-4'-carboxamide). active ingredient of Dipiperon (Janssen-Cilag B.V), administered to a patient in a dose ranging between 8 and 12 mg is claimed via its specific pharmacological properties to be a booster of the effect of the selective serotonin re-uptake inhibitor citalogram towards OCD. Preferably, pipamperon is administered daily at least 4-5 days before administering said antidepressant. The mechanism of boosting of pipamperon has to 10 deal with (i) the selective affinity for the dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) the selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors. This semi-naturalistic open label study investigated the efficacy 15 and tolerability of the combo pipamperon - citalopram in the treatment of patients with OCD.

### **Details**

Design:

Semi-naturalistic i.e. inclusion of every 'natural' patient in an outpatient

practice but without concomitant use of mood enhancing drugs, open

label

Control:

No

Phase:

Phase IIa - preliminary Proof of Concept

Location:

Belgium - Research Centre ANIMA, Alken

End Points:

Assessment scale scores, Yale-Brown Obsessive-Compulsive Scale,

Reduction, Remission

Medication:

Exclusion of mood stabilisers, antipsychotics (typical and atypical) and

other antidepressants

\_ . . .

20

### Subjects

Туре	No.	Sex	Age
Patients	7	1 male & 7 female	20-63 (mean 33) years

Characteristics: patients had an obsessive-compulsive disorder according to DSM-IV criteria, with or without a chronic course and a treatment refractory state towards another SSRI then citalopram.

### 5 Treatments

10

15

PIP-CIT<sup>1</sup> ADD-ON: citalopram from DAY minus 730-60 - pipamperon from DAY 0

Drug/Treatment	Dose			Rou	ite Freque	ency Duration
Pipamperone <sup>1</sup> Citalopram <sup>1</sup>	+ Pip.: 8-16 mg/day	mg/day	- Cit.:	30-80 PO	bid	12 weeks

1. Pipamperone (Pip) and Citalopram (Cit) dosage was adjusted according to clinical response.

PIP-CIT<sup>1</sup> FORE-GOING 4-6: pipamperon from DAY 0 - citalopram from DAY 4-6

Drug/Treatment	Dose	Rout	e Freque	ncy Duration
Pipamperone <sup>1</sup> Citalopram <sup>1</sup>	+ Pip.: 8-16 mg/day - mg/day	Cit.: 30-80 PO	bid	12 weeks

1. Pipamperone (Pip) and Citalopram (Cit) dosage was adjusted according to clinical response.

### Results

5

	PIP-CIT add-on after 730-60 DAYS (mean 241) (n = 6) with mean Cit. 54mg/d and Pip. 11mg/d	
	PIP-CIT foregoing 4-6 DAYS (mean 5) (n = 2) with mean Cit. 60mg/d and Pip. 10mg/d	
Y-BOCS score		
Baseline		
Total	31	
Obsessions	18	
Compulsions:	13	
Endpoint (week 12)		
Total	<u>15</u>	
diminishment	-16 (+16/-11)	
% reduction	53	
Obsessions		
total	8 .	
diminishment	-10 (+9/-7)	
% reduction	57	
Compulsions		
total	7	
diminishment	-6 (+7/-6)	
% reduction	45	
% Remission		
YBOCS score ≤8	29	
BOCS score ≤16	57	

Notably, the results obtained are highly significant since the variability in every group is distributed evenly around the mean.

Figure 12 schematically depicts the Y-BOCS total score: "fore-going" and "add-on" treatment with pipamperon (8-15 mg/day; bld) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-

15

20

25

citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003).

Figure 13 schematically depicts the Y-BOCS obsession score: "fore-going" and "add-on" treatment with pipamperon (8-15 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003).

Figure 14 schematically depicts the Y-BOCS compulsion score: "fore-going" and "add-on" treatment with pipamperon (8-16 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003):

The intention-to-treat / last-observation-carried-forward analysis showed a high therapeutic efficacy according Y-BOCS total score, obsession and compulsion scores. This indicates the boosting effect of pipamperon on the SSRI citalogram at an extremely and thus unconventional low dose. No patient discontinued treatment.

### Assessment

Efficacy: the combo pipamperone 8-16mg/d - citalopram 30-80mg/day > the in the art known compounds effective towards OCD (Hollander E, Koran LM, Goodman WK, Greist JH, Ninan PT, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. Journal of Clinical Psychiatry 64: 640-647, Jun 2003 Mount Sinai School of Medicine, New York, New York, USA; Solvay Pharmaceuticals Inc., Marietta, Georgia, USA).

### 30 Study Messages

The boosting effect of pipamperon at an extremely unconventional low dose on a SSRI is indicated since the efficacy of the 'add-on' and 'fore-going' combo 'pipamperon 8-15 mg/d - citalopram 30-80 mg/day' is in this study as twice higher as known in the art in the treatment of patients with obsessive-compulsive disorder.

# Example 5: combo pipamperon-citalopram: therapeutic use in Panic Disorder.

### Purpose

Preliminary examination of a "fore-going" and "add-on" treatment with pipamperon and citalogram in comparison with the SSRI in Panic Disorder.

### Results

The results are indicated in Figure 15. Figure 15 schematically depicts the CGI-severity score: "fore-going" and "add-on" treatment with pipamperon (8 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SSRI in Panic Disorder. Treatment with the combo pipamperon-citalopram (n = 3). Treatment with paroxetine is according to the Journal of Clinical Psychiatry (2004) 65: 405-413. Treatment with Sertraline is according to the Journal of Clinical Psychiatry (2004) 65: 405-413.

### 15 Conclusion

Notably, although a small test group has been used (n = 3), the distribution around the mean is good. It will further be apparent from Figure 15 that the effect of the combo treatment of pipamperon and citalopram is twice as high as the standard treatments with paroxetine or sertraline.

20

35

10

## Example 6: POC process for mayor depressive disorder

Concept: Combo of the high selective 5-HT2A/D4 antagonist pipamperon with:

- a compound active towards the Amino Acid Transmitter, Peptidergic Transmitter,
   Adenosine Transmitter, Endocrine and/ or Enzymatic System;
  - a fore-going admission during 4 days of pipamperon;
  - a dose of pipamperon of 12 mg/day

# 30 Objectives: Demonstrating that this combo the primas:

- the potency of being a treatment standard for depression by having an added value of reducing the total score of the Hamilton Depression Rating Scale – 17 items (HDRS-17) after 8 weeks of therapy with a least 20% more than reached with the conventional known antidepressants, i.e. 60% versus 40%. This stands for an added medium demission of 5 points on the total score of the HDRS-17 and by this will be very highly

25

30

significant since the mean difference in all recent clinical trials between placebo and active treatment is 2.5;

- a more sustained therapeutic effect than the conventional mono therapy by preventing significant more relapses during 48 weeks following the acute treatment; and/or
- a complete neutral safety profile, e.g. there are no more adverse events in the combo therapy then in mono admission of the in the combo used antidepressant compound.

<u>Process</u>: the following different steps were implemented to reach out for these objectives (see also Tables 3 and 4):

- (1) an naturalistic open label study (n=>20) on a depressive population with a normal variability of medical and psychiatric history, course of depression, earlier and concomitant therapy admitting the golden standard antidepressant citalopram 20-40 mg/day and a dose of 8-12 mg/day of pipamperon in a foregoing, simultaneous or add-on use.
- 15 (2) a 16 weeks placebo controlled randomised four armed study of each 36 patients with a mayor depressive disorder admitting:
  - from day 0: placebo or pipamperon (PIP) 10 mg/day or an active antidepressant compound or the combination of the last two;
  - from day 4: placebo or pipamperon 10 mg/day combined with an active antidepressant compound or an active antidepressant compound without pipamperon.

By including rigorous control groups (placebo and active comparator; see Tables 3 and 4) this clinical trial is evaluated as a proof of concept of the added value of the combo and the foregoing treatment method since the inclusion/exclusion of:

- a negative trial, i.e. no significant difference between the placebo and active treatment with the comparator;
- a failed trial, i.e. no significant difference between the active and the studied treatment i.e. the combo.
- (3) an active controlled randomised relapse prevention study following the POC trial during another 36 weeks with three arms of each 36 patients which is formed by:
  - continuation of the active mono therapy;
  - randomising the patients with a combo therapy in a group with an active mono therapy and with a continuation of the combo treatment.

ר'י - הדה ה החר

#### Claims

- 1. Use of pipamperon for the preparation of a medicament for treating a disease or disorder with an underlying dysregulation of the emotional functionality, wherein said pipamperon is administered to a patient in a dose ranging between 5 and 15 mg of the active ingredient, and wherein a second compound is administered simultaneously with, separate from or sequential to said pipamperon to augment the therapeutic effect of said second compound.
- Use according to claim 1, wherein said pipamperon is administered daily at least
   one day before administering said second compound.
  - 3. Use according to any of claims 1 to 2, wherein said second compound affects the monoaminergic tansmitter system.
- 15 Use according to claim 3, wherein said second compound is selected from the group comprising: 5-HT reuptake enhancer (1), 5-HT1 autoreceptor agonist (2), 5HT1A receptor agonist (3), 5-HT1A receptor antagonist (4), 5-HT1B receptor antagonist (5), 5-HT2B receptor antagonist (6), 5-HT2C receptor antagonist (7), 5-HT3 receptor antagonist (8), 5-HT6 receptor antagonist (9), adrenergic transmitter releaser (12), α1 adrenoreceptor antagonist (13), α2 adrenoreceptor antagonist (14), β3 adrenoreceptor agonist (19), 20 cannabioid receptor antagonist (21), D1 receptor agonist (27), D2 receptor antagonist (28), D3 receptor antagonist (29), DA uptake inhibitor (30), dopamine receptor agonist (31), H3 receptor antagonist (42), compounds which increase brain concentrations of 5-HT (44), levodopa (48), MAO reuptake inhibitor (50), MAO-A & MAO-B reuptake inhibitor 25 (51), MAO-B inhibitor (52), MAO-B re-uptake inhibitor (53), NARI (60), NaSSA (61), NDRI (62), RIMA (82), SDA (84), SDRI (85), Second messenger beta agonist (86), SNDRI (90). SNRI (91) and SSRI (92).
- 5. Use of pipamperon or a pharmaceufically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial

behaviour, bereavement, occupational problem and problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 10 6. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome. somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, 15 impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of 20 a 5-HT1 autoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1 autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 25 7. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome. somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse 30 control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to 35 head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A) receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin) 1A receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 10 8. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, 15 attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A receptor antagonist compound to augment the therapeutic effect or to provide a faster 20 onset of the therapeutic effect of sald 5-HT1A receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 25 9. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse 30 control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1B receptor antagonist compound to augment the therapeutic 35 effect or to provide a faster onset of the therapeutic effect of said 5-HT1B receptor

:+3292802345

5

10

15

20

25

30

antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 10. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2B receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2B receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 11. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2C receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 12. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance-related disorders, characterized in that pipamperon or said pharmaceutically

10

15

20

25

30

35

213

acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 13. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT6 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT6 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 14. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

20

25

10

5

16. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

35

17. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders,

30

35

215

impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 10 18. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, 15 disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, pain disorders and delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate 20 from or prior to the administration of a cannabioid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabloid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active 25 ingredient.
  - 19. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

25

30

35

..... MA MANA MOET

- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 20. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, pain disorders and delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 21. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 22. Use of pipamperon or a pharmaceutically acceptable sait thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with,

10

15

20

25

**30** 

35

separate from or prior to the administration of a DA (dopamine) uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA (dopamine) uptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 23. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders and problems related to abuse or neglect, pain disorder and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 24. preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment ... disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a histamine H3receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said histamine H3receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

25

30

- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 25. preparation of a medicament for treating the underlying emotion dysregulation of a non cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome. somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases brain concentrations of 5-HT (serotonin), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 26. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a levodopa/decarboylase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said levodopa/decarboylase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 27. A pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboylase inhibitor compound, preferably is (eti)levodopa/carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.
- 35 28. A pharmaceutical composition according to claim 27, wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein

20

said levodopa/decarboylase inhibitor compound is levodopa/carbidopa, preferably provided in a unitary dose of between 100 mg and 10 mg of the active ingredient.

- 29. A pharmaceutical composition according to claim 27 or 28, wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboylase inhibitor compound is levodopa/carbidopa or etilevodopa/carbidopa in combination with entacapone, of which the latter is preferably provided in a unitary dose of between 500 mg and 100 mg of the active ingredient.
- 30. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of non-cognitive mental disease or disorder which are substance related disorders and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 31. preparation of a medicament for treating the underlying emotion dysregulation of a non cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative 25 disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of 30 a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active 35 ingredient.

10

15

20

25

30

35

EPO MUNCHBN

- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 32. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 33. preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) reuptake inhibitor to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) reuptake inhibitor, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 34. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective noradrenaline re-uptake inhibitor (NARI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake

10

15

inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 35. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissoclative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 20 36. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that 25 pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective noradrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized 30 in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 37. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders

-1.

Fmof --:+01/10/0001 99.EQ

consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

10

15

20

25

30

- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 38. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorder and delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 39. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-

related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine re-uptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine re-uptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

20

25

10

5

Use of pipamperon or a pharmaceutically acceptable salt thereof for the 40. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, control disorders. substance-related disorders, personality bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

35

41. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-

deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

5

Use of pipamperon or a pharmaceutically acceptable salt thereof for the 42. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attentiondeficit disorders, substance-related disorders, personality disorders, antisocial behaviour. bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable sait thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25

30

35

43. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin

- 11 - 120 D 04

re-uptake inhibitor (SSRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

30

- 44. Use according to claim 1 or 2, wherein said disease or disorder is Alzheimer disease.
- 45. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 46. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT6 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT6 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
  - 47. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an acetylcholinesterase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said acetylcholinesterase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

35

- 48. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 49. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an amyloid aggregation-inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said amyloid aggregation-inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 50. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
  - 51. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a choline uptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said choline uptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 1, -030 D 04

52. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound that activates ERK (extracellular signal-related kinase) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound that activates ERK (extracellular signal-related kinase), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

5

53. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzhelmer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

•

25

20

54. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a histamine H3-receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said histamine H3-receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

35

55. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases insulin sensitivity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases insulin sensitivity, further characterized in that pipamperon is to be

10

228

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 56. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 57. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a muscarinic receptor partial agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said muscarinic receptor partial agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 58. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 59. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable

ר ... יפשט D A40

salt thereof is administered simultaneously with, separate from nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 60. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 61. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 62. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a non-steroidal anti-inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 35 63. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of

5

10

15

20

25

10

15

20

25

30

35

Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active Ingredient.

- 64. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
  - 65. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
  - 66. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- י אישט ה טבט

10

15

20

25

30

35

- 67. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 68. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 69. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

15

20

25

30

35

- 70. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, disorders, substance-related disorders, personality disorders, impulse control bereavement, occupational problem and problems related to abuse or neglect. characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 71. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, disorders, substance-related disorders, personality impulse control bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 72. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep

10 .

15

20

25

30

35

ł

disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 73. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrial syndrome, somatoform disorders (excluding pain disorders), fartitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, control disorders, substance-related disorders, personality bereavement, occupational problem and problems related to abuse or neglect, characterized in that piparaperon or said pharmaceutically acceptable sait thereof is.administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 74. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable

10

15

20

25

30

35

salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

EPO Munchen

- Use of pipamperon or a pharmaceutically acceptable salt thereof for the **75**. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- Use of pipamperon or a pharmaceutically acceptable salt thereof for the 76. preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders. disorders, substance-related disorders, personality disorders, control bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a substance P receptor (NK1) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

235

77. Use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a noncognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders. impulse control disorders, substance-related disorders, personality bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a tachykinin antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

78. Use according to any of claims 1 to 4 or 7, wherein said second compound is gepirone.

- 79. A method for preparing a compound having a selective D4 and 5-HT2A antagonist. reverse agonist or partial agonist activity comprising the following steps: (a) measuring the 20 selective affinity of a test compound to the D4 receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the D4 receptor in respect to all the other D receptors, and measuring the selective efficacy of the selected compound to the D4 receptor and selecting a compounds which is a selective antagonist, inverse agonist or 25 partial agonist of the D4 receptor; (b) measuring the selective affinity of a test compound to the 5-HT2A receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the 5-HT2A receptor in respect to all the other 5HT receptors, and measuring the selective efficacy of the selected compound to the 5-HT2A receptor and selecting a compounds which is a selective antagonist, inverse agonist or partial agonist of the 5-HT2A receptor; (c) identifying a compound which is selected in (a) and (b), (d) 30 preparing the compound identified in (c).
  - 80. Compound prepared by the method of claim 79.
- 35 81. Use according to any of claims 1, 2 or 7, wherein said second compound is chosen from the group consisting of fluvoxamine controlled release, phenserine tartrate,

10

atomoxetine hydrochloride, bupropion (controlled-release formulation), ropinirole HCL (controlled-release formulation), INN 00835, galantamine (extended release formulation), paliperidone, tornoxetine, aprepitant, rivastigmine tartrate, ORG 34517/34850, sunepitron, sumanirole, milnacipran, idazoxan, xaliproden, SR 58611, befloxatone, litoxetine, tianeptine, agomelatine, SPD 503, flesinoxan, bifeprunox, ramelteon, etilevodopa, rasagiline (TVP-1012) and desvenlafaxine.

82. Use according to any of claims 1, 2 or 7, wherein said second compound is chosen from the group consisting of galantamine (extended release formulation), R121919, risperidone, paliperidone and R228060 (YKP-10A).

- }'

### **Abstract**

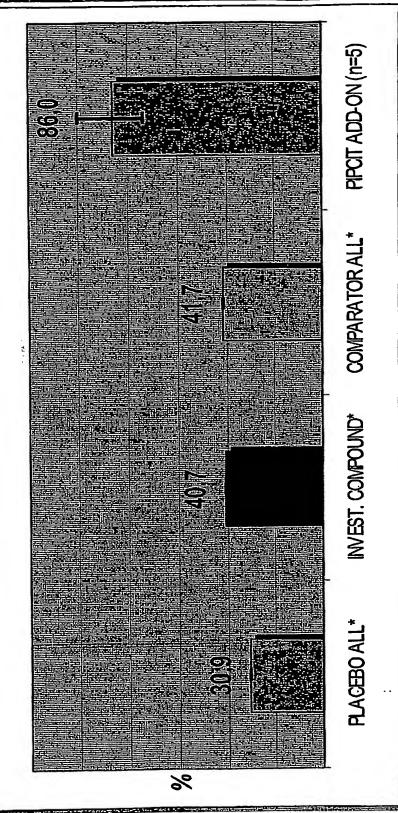
5

10

The present invention relates to the use of compounds and compositions of compounds having D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity for the treatment of the underlying dysregulation of the emotional functionality of mental disorders (i.e. affect instability – hypersensitivity – hyperaesthesia – dissociative phenomena – etc). The invention also relates to methods comprising administering to a patient diagnosed as having a neuropsychiatric disorder a pharmaceutical composition containing (i) compounds having D4 antagonistic, partial agonistic or inverse agonistic activity and (ii) compounds having 5-HT2A antagonistic, partial agonistic or inverse agonistic, and (iii) any known medicinal compound and compositions of said compounds. The combined D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic effects may reside within the same chemical or biological compound or in two different chemical and/or biological compounds.

Id-On Treatment with Pipamperon 8-12 (mean 9) mg (bid) after Treatment Inparison with the Standard Efficacy of Antidepressants in Clinical Trials\* (PIPCIT ADD-ON) with HDRS-17 Totalscore = 29 at Baseline in MDD in with Citalopram 10-20 (mean 30) mg (bid) during 20-60 (mean 33) days

# HDRS-17 REDUCTION OVER 8 WEEKS IN MDD



KHAN et al, Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinica



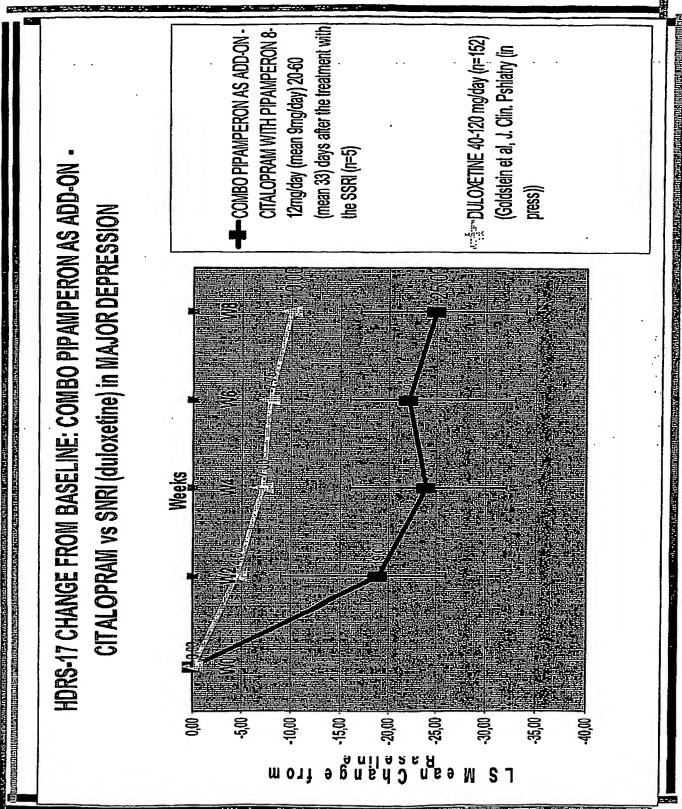
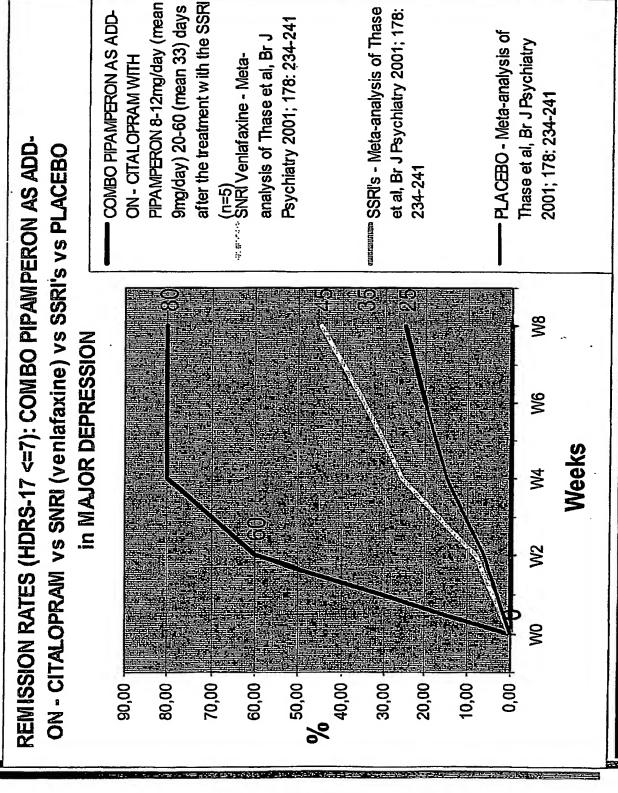


Figure 2

3/15



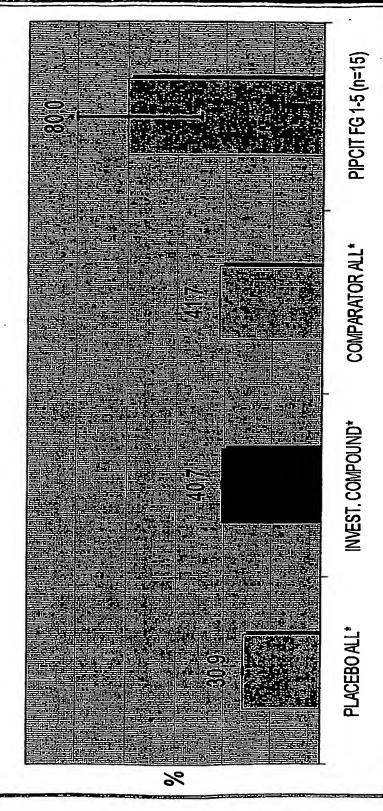
ri fi

Figure 3

4/15

g/day (bid) Followed With the Combination Treatment of Pipamperon and Citaloprar 20-50 (mean 26) mg/day (bid) (PIPCIT FG 1-5) in MDD (HDRS-17 at BL = 23) in Foregoing Treatment During 1-5 (mean 4) days with Pipamperon 8-12 (mean 10) Comparison with the Standard Efficacy of Antidepressants in Clinical Trials\*

# **HDRS-17 REDUCTION OVER 8 WEEKS IN MDD**



KHAN et al, Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical

The State of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Comp

Figure 4

....

•

----

WITH PIPAMPERON 10mg/day vs SNRI (duloxetine) in MAJOR

CITALOPRAM WITH A FORE-GOING TREATMENT OF 4 DAYS

HDRS-17 CHANGE FROM BASELINE: COMBO PIPAMPERON-

3/15

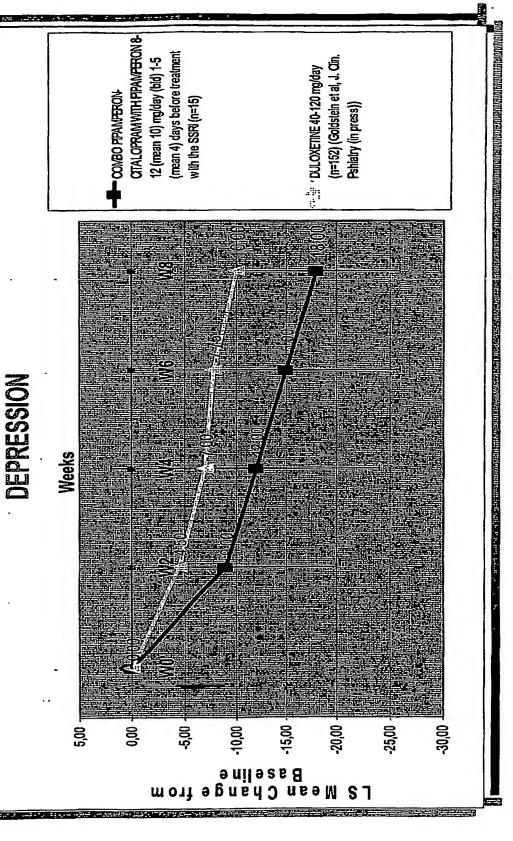


Figure 5

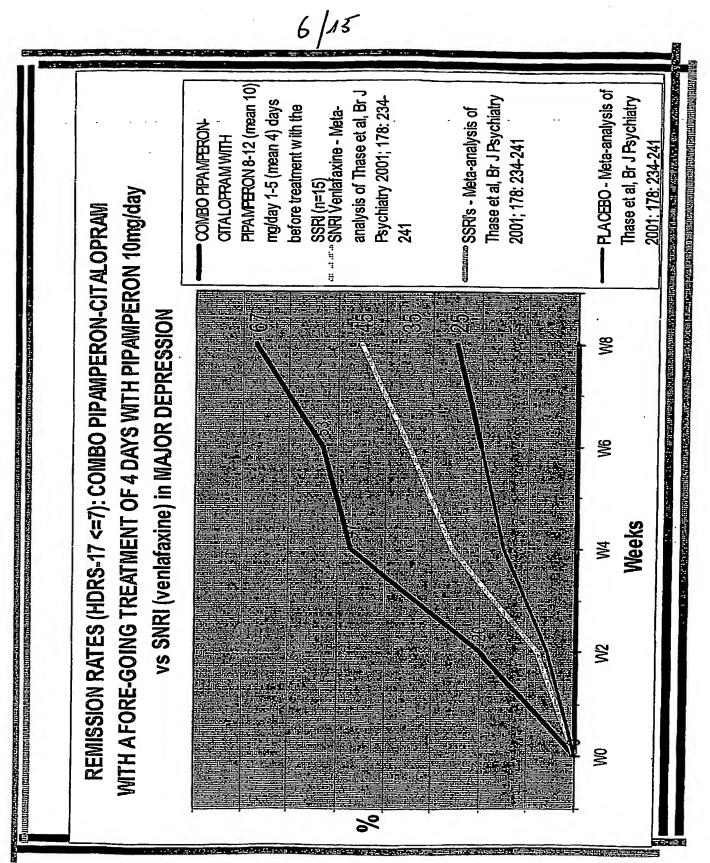


Figure 6

&. KHAN et al, Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinica

THEIS FRUETTE FEETNERS FOR STANFORD AND PROPERTY OF STANFARMENT OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF STANFORD OF

Foregoing Treatment During 6-8 (mean 7) days with Pipamperon 8-12 (mean 14 ng/day (bid) Followed With the Combination Treatment of Pipamperon and Citalopra 20-40 (mean 30) mg/day (bid) (PIPCIT FG 6-8) in MDD (HDRS-17 at BL = 28 in Comparison with the Standard Efficacy of Antidepressants in Clinical Trials\*

HDRS-17 REDUCTION OVER 8 WEEKS IN MDD

PIPCIT FG 6-8 (n=3) COMPARATOR ALL\* INVEST. COMPOUND\* PLACEDO ALL'

Figure 7



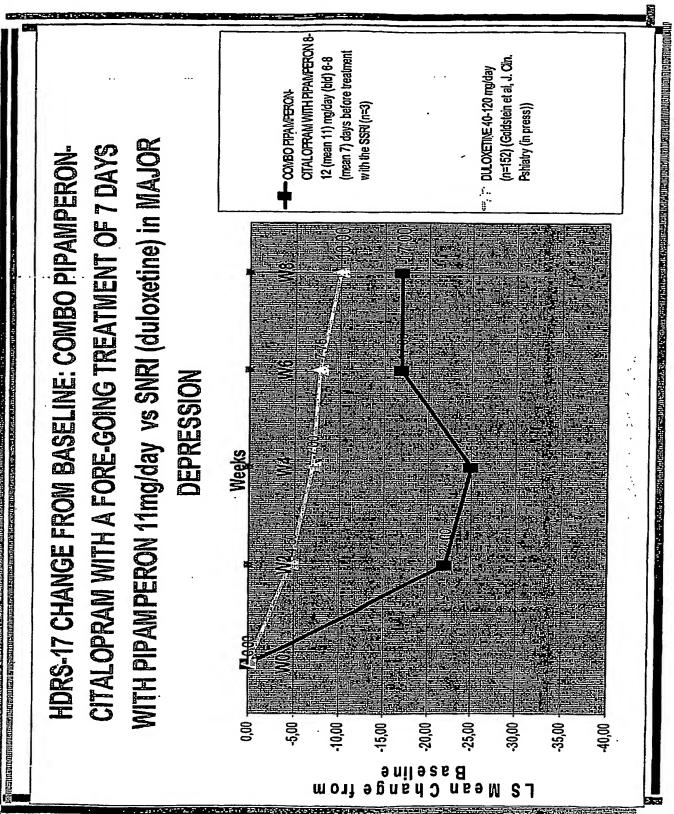


Figure 8

rrials, ARCH. OF GENERAL PSYCHIATRY / VOL 57, APR 2000)

Foregoing & Add-On Treatment with Pipamperon 8-12 mg/day (bid) and Citalopram 20-40 mg/day (bid) in MDD in Comparison with the Standard Efficacy of Antidepressants in Clinical Trials\*

HDRS-17 REDUCTION OVER 8 WEEKS IN MDD

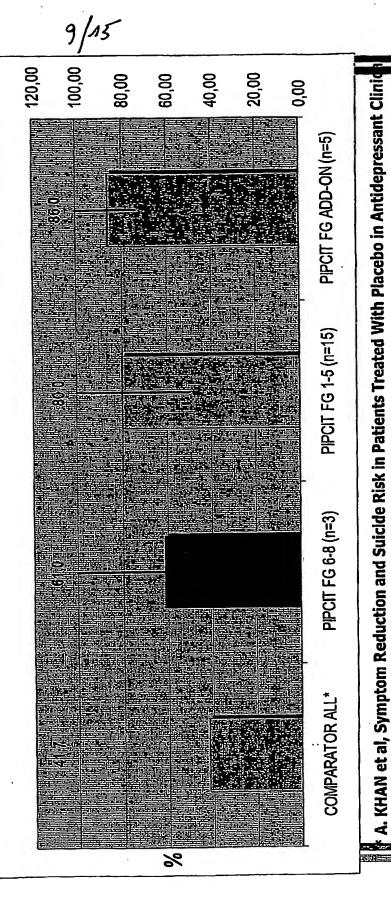


Figure 9

\_ \_ \_\_\_\_

10/15

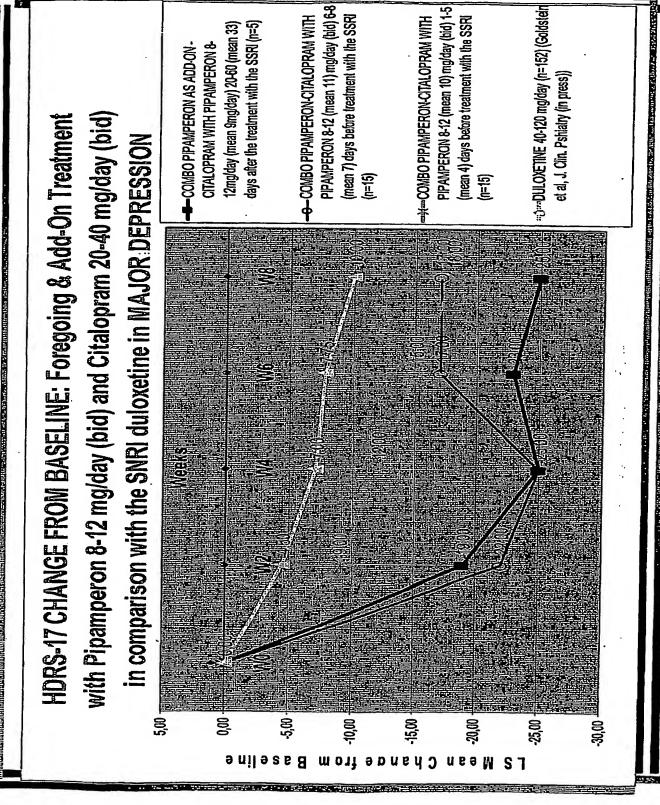


Figure 10

M/15

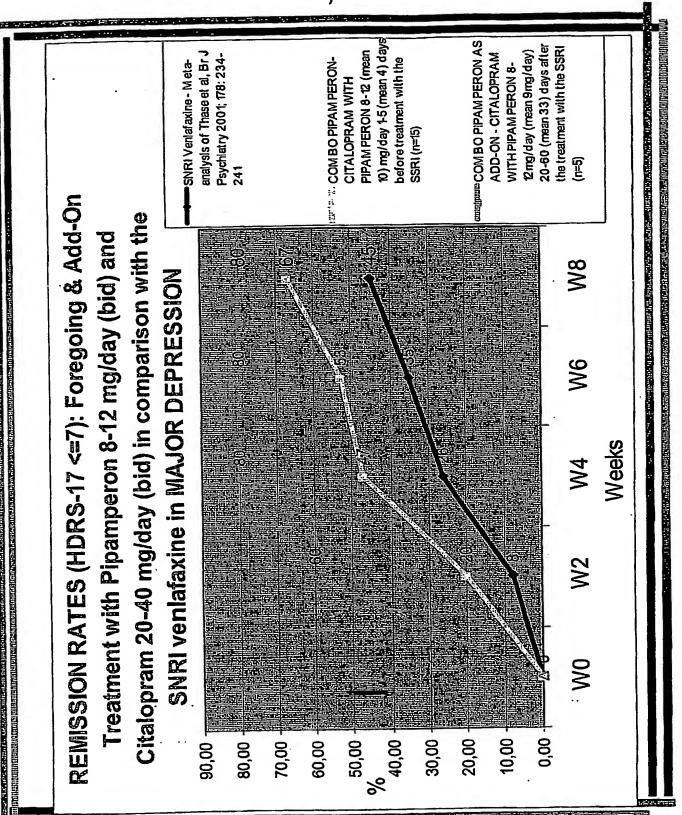


Figure 11

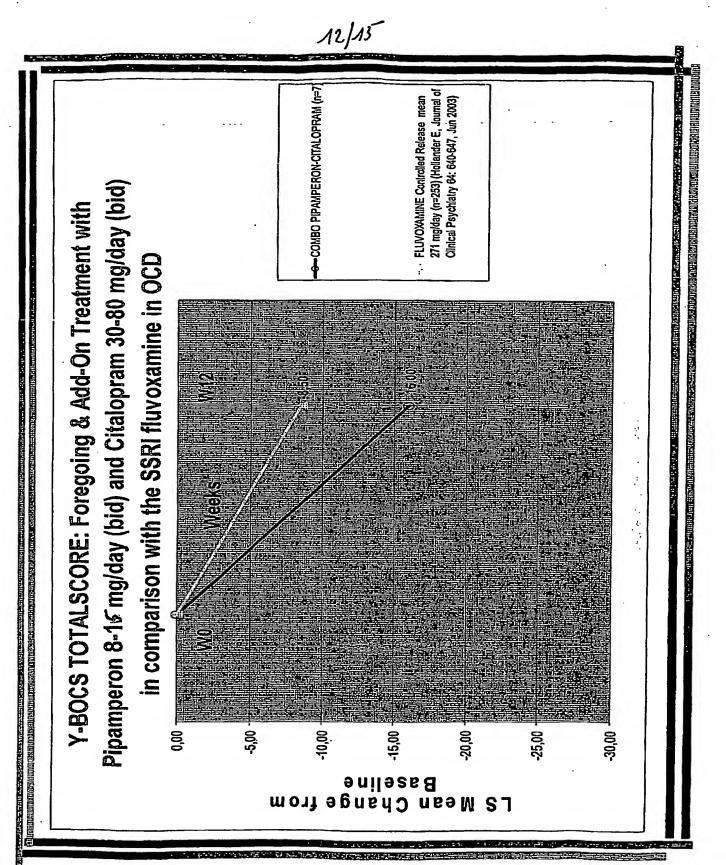


Figure 12

E-m/ 1, 2, 10004 01:07

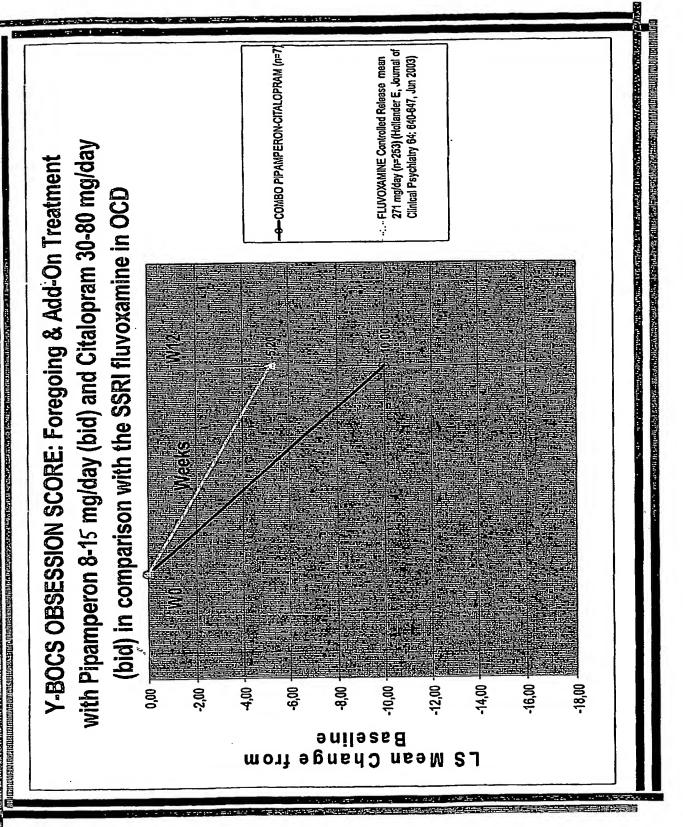


Figure 13

14/15

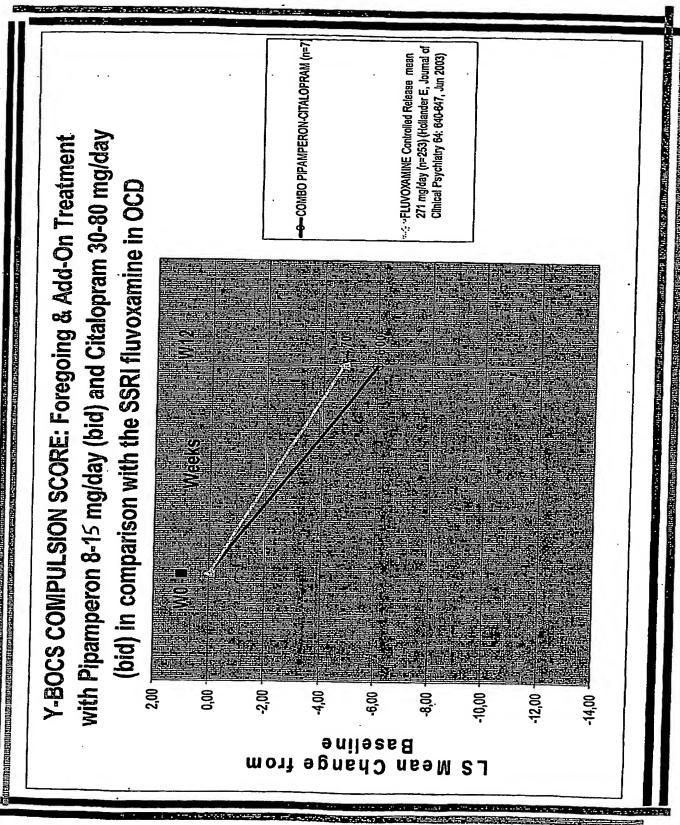


Figure 14

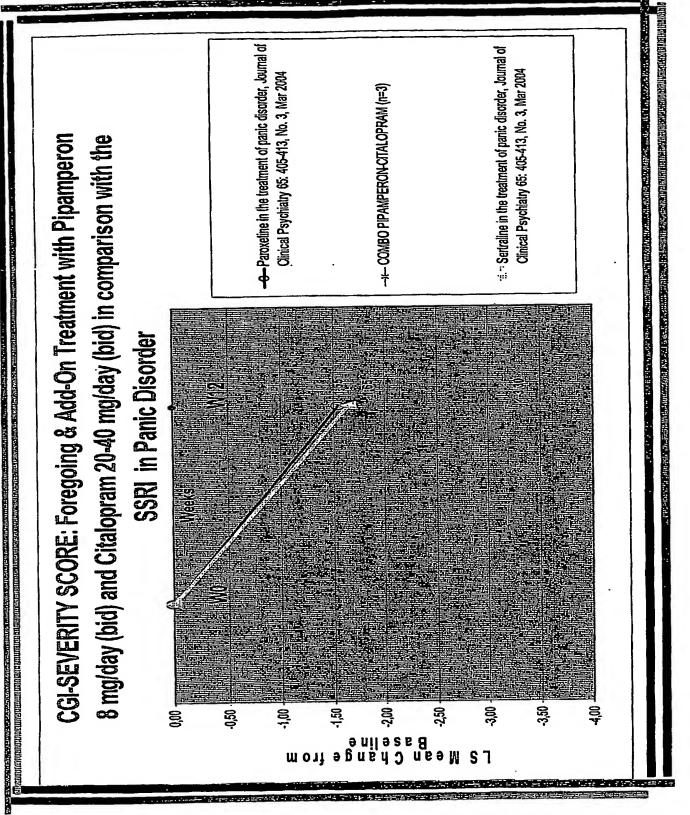


Figure 15

# Document made available under the **Patent Cooperation Treaty (PCT)**

International application number: PCT/BE04/000172

International filing date:

02 December 2004 (02.12.2004)

Document type:

Certified copy of priority document

Document details:

Country/Office: EP

Number:

04025035.9

Filing date:

21 October 2004 (21.10.2004)

Date of receipt at the International Bureau: 14 April 2005 (14.04.2005)

Remark:

Priority document submitted or transmitted to the International Bureau in

compliance with Rule 17.1(a) or (b)



# This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

### **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

□ BLACK BORDERS
□ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
□ FADED TEXT OR DRAWING
□ BLURRED OR ILLEGIBLE TEXT OR DRAWING
□ SKEWED/SLANTED IMAGES
□ COLOR OR BLACK AND WHITE PHOTOGRAPHS
□ GRAY SCALE DOCUMENTS
□ TINES OR MARKS ON ORIGINAL DOCUMENT
□ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

## IMAGES ARE BEST AVAILABLE COPY.

☐ OTHER:

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.